Phyto-Therapeutic Potential and Pharmaceutical Impact of Shilajit (Asphaltum punjabianam): Current Research and Future Prospects

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Abstract

Shilajit, derived from India, is a naturally-occurring mineral substance with a range of components, utilized in the medicinal practices of both Ayurveda and Siddha traditions.Shilajit has been employed for its phytomedicinal effects in addressing various ailments, as well as for nutritional purposes. Shilajit contains rich source of humic substances (like fulvic acid, humic acid), among the over 20 elements it contains are calcium, magnesium, sodium, iron, chromium, and lead. Additionally, it contains hydrocarbons, proteins, carbohydrates, fatty acids, amino acids, and alcohols. Furthermore, about 15-20% of minerals are also present. The diverse range of phytochemicals present in them imparts a more potent impact on human health, coupled with significant antioxidant capacity. Presently, it is being proposed as a potential source for various unique industrial and medicinal products. In literature, a wealth of data provided about geographical description, herb interaction, therapeutic intervention, nanotechnology on and combined approaches Formulation strategies. In this review, there is a comprehensive presentation of information encompassing the phytochemical significance, pharmacology, pharmaceutical impact, and the potential applications in nanotechnology, along with the nutraceutical values of shilajit.

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Introduction

The World Health Organization defines traditional medicineas the application of herbal, animal and mineral based remedies, either separately or in synergy, to cure and prevent diseases and preserve health [1]. Eighty percent of the world's population, according to WHO estimates, receives their medical treatment from traditional practitioners [2]. Consequently, there is a growing global research focus on plant-based medicine while neglecting the other two pillars of conventional health: animal- and mineral-based medicine. Shilajit is the particular mineral that is the subject of this essay. Shilajit is a commonly utilized natural mineral in the Siddha pharmacopoeia, it enumerates 220 metal and mineral compounds utilized in conventional Indian medical systems [3]. Though there are references to shilajit in traditional literature, most Westerners are today ignorant of it. The importance of shilajit has expanded significantly over the past 3,000 years since it has been a crucial part of traditional Indian medicine, Tibetan pharmacology, and the traditional medicine of the formerSoviet Union [4]. The Indian Ayurvedic and Siddha therapies offer two primary advantages: an improved quality of life and enhanced resistance to sickness. Shilajit, classified as a rasayana in these traditional systems, is believed to contribute to these benefits [5].

Shilajit (Asphaltum) a naturally occurring, multi-component mineral that originated in India and was utilized in the Ayurvedic and Siddha medical systems [6]. Ayurvedic medicine has been using shilajit for millennia as a rejuvenator and antiaging ingredient. In traditional Indian Ayurvedic medicine, a rasayana substance has two key functions: it strengthens the body and improves human health [7]. A rock exudate known as shilajit may be found in sedimentary material of the Himalayan, Altai, and other mountain ranges. In Ayurveda, it is considered a maharasa, or super-vitalizer. It is the main component of a large number of nutritional supplements available today. It also contains fulvic acids, over 40 minerals, and release and conjugated dibenzo-α-pyrones [8]. In the Himalayas, from Kashmir in the west to Arunachal Pradesh in the east, shilajit is frequently establish. Additionally, it may be found in other nations such as Bhutan, Nepal, Pakistan, China, Tajikistan, Australia, Afghanistan, Tsao-Shing and India [9][10][11][12][13][14].

In classical literature, Lord Shiva described how the drug's origins sprang from the summertime heating of the mountains, which in turn released the extract known as Shilajit, which is Dhatu's exudate. Hindus believe that in the high-altitude Himalayan hills, there are Sadhus and Yogis whom the living and mediating for hundreds of years without ever becoming ill or elderly. Many people claim to have encountered these people. They consume what are known to be Shilajit ingredients, which enable them to endure severe weather conditions with little to no warm clothing and to stay youthful and energetic throughout. Shilajit is said to be the "Amrit" that Lord Shiva gave humanity, giving them endless youth and health. Charaka and Susruta claim that heat was produced and a significant amount of perspiration was made during the Samudra Manthan (ocean churning) event between Gods and Demons owing to friction. The gods regarded perspiration and nectar as divine substances. Shilajit (shila: mountain + jit: winner) is the term given to the divine medication that was given in little amounts to the mountains. However, the substance melted under the sun's rays and took on the appearance of lac or jatu. According to Ayurveda, Shilajit originated Flowing from the mountains due to the intense heat of the

sun, [15][16][17].

Plant sap, or latex juice, is said to exude as a sticky exudate that emerges from the rocky surfaces of the mountains. Between May and June due to the extreme heat of the sun, according to the ancient Rasarangini and Sushruta Samhita scriptures. Furthermore, Dwarishtarang and Rasarangini explain that shilajit is an exudate of plant gum resin latex, etc. that originates from the rocks of mountain when extreme heat is present. Claims indicate that certain species of mosses, like Fissidens, Barbula, Minium, and Thuidium, as well as specific liverwort species like Dumortiera, Marchantia, Pellia, Plagiochasma, Stephaniella, and Asterella play a role in the formation of shilajit. The creation of shilajit is attributed to bryophytes known as anthroperos, which are found near rocks that exude shilajit [10]. It is increasing the effectiveness of Terminalia chebula (myrobelan), cordifolia (bala), Terminalia tomentosa (asana), Catechu nigrum (catechu), Bachanania lactifolia (piala), Acacia fernesiana (acacia) and Shoria robusta (sala) in the decoction form [18]. Shilajit, a light brown to dark brown exudate with varying consistencies, is found between 1000 and 5000 meters above sea level in sedimentary rocks of various strata all over the world [19].

Currently, the pharmaceutical industry is undergoing a significant transformation, moving away from dependence on synthetic compounds to adopting natural sources obtained from plants, animals, or minerals for disease management. The utilization of medications for illness management has experienced substantial growth. Historically, all medicines were extracted from plants. The plant kingdom still contains numerous species holding medicinal and nutraceutical chemical constituents that remain undiscovered. Fruits and vegetables serve as a valuable repository, offering a diverse range of nutritional compounds. Contemporary pharmaceutical industries necessitate large quantities of authentic plants for drug manufacturing. The extraction of the active ingredients and the production of medicine composition (formulation) entail advanced technologies and demand substantial capital investment, providing attractive remuneration [20].

This study focuses on new research on the active components, pharmacological properties, and biological activities of phytoconstituents. Medicinal benefits of shilajit, and numerous aspects of drug delivery's impact. It underscores the potential and broad scope of combined herbal therapy.

Synonyms

Synonyms play a crucial role in traditional Indian medicine because they effectively communicate the unique qualities of each medication. The terms "derived from rock" (shilajatu, shilaras, adrija, and girija) are used in Sanskrit. Arabic arakul-dzhibol means "sweat of the mountain," whereas Burmese kao-tui or chao-tui denotes "blood of the mountains" and Tibetan or Mongolian brag-shun or bragzhun means "juice of rock." [21][22]. Table 1 contains a list of synonyms for "shilajit."

Table 1. Contains a list of Synonyms of shilajit

Language	Name	Reference
Sanskrit	Silajit, Shilajit, Silaras	[23]
Hindi and Marathi	Silajita	[24]
Hindi	Shilajit	[23]
Tamil	Uerangyum, Perangyum, Uerangyum	[23]
Arabic	Hajar-ul-musa	[23]
English	Asphalt, Mineral Pitch	[23]
Persian	MomiaiFaqurualYahud	[24]
Russian	Mummio, Mumie	[23]
Latin	Asphaltum	[25]
Bengali	Silajatu	[23]
Greek language	Bitumen mineral	[26]

Therapeutic use in traditional system

Shilajit has been shown to have antiseptic, analgesic, deobstruent, germicidal diuretic, expectorant, laxative, tonic, anti-bilious, immunomodulator, and lithotriptic characterstics when applied topically. This information is derived from customary Indian wisdom. Shilajit is recommended in conjunction with milk to manage diabetes, and with Commiphora wightii (Arn.) Bhand (guggulu) to cure breaks [27][10]. Fulvic acid seems to have potential as a preventive measure against Alzheimer's., given its ability to stop tau from self-aggregating into pathogenic filaments. Traditionally, people from Nepal and northern India have incorporated shilajit into their diets, often mixing it with milk as part of their breakfast. The Sherpas are a group of strong guys who live exceptionally long lives and who say they eat shilajit in their diet. Our findings demonstrate the Andean version of shilajit's exceptional effectiveness in treating cognitive issues and enhancing cognitive function in humans [28]. Shilajit is included in the rasayana class in the Charaka Samhita, the earliest written work in the Ayurvedic healthcare system. Charaka states that shilajit, when combined with other drugs, can be used as an adjuvant and anupana (vehicle) to treat a wide range of ailments. Sushruta explains shilajit (diabetes mellitus) in his Madhumeha Chikitsa. He suggests using pure shilajit and an infusion of the Shorea robusta group of plants for madhumeha [29]. Shilajit's organic components function as a synergistic booster of other drugs because they play a part in the transit of several mineral compounds to their cellular destinations [30].

Chemical composition

The three main chemical components that make up Shilajit are as follows and listed in Figure 1: (1) Dibenzo-pyrones-chromo proteins (DCPs) with medium and high molecular weights that include coloring agents like carotenoids and

indigoids as well as trace metal ions. (2) low and non-humic organic molecules with a medium molecular weight, which include dibenzo-pyrones and their conjugates (fatty acyl, amino-acyl, and lipoidal groups). (3) fulvic acids and fusims, which are metallo-humates with dibenzopyrones in their core nucleus [31]. Shilajit contains 20 to 40% minerals and 60 to 80% organic materials. In addition, 65 chemical compounds, including amino acids, waxes, resins, polyphenols, essential oils, free fatty acids, coumarins, albumins, and organic acids like citric, tartaric, oxalic, succinic, and adipic are included,major phytochemical and their activities listed in Table 2 [21]. The raw material contains fulvic acid, humic acids, essential fatty acids, amino acids, gums, proteins, waxes, steroids, and vitamins. It also contains a lot of minerals, such as potassium, magnesium, and calcium [32]. A processed shilajit usually comprises fulvic acid and its equivalents, 0.3-0.4 percent dibenzo-α-pyrones, 10-30 percent DBP chromo-proteins and mineral substances (10-15%) [8].

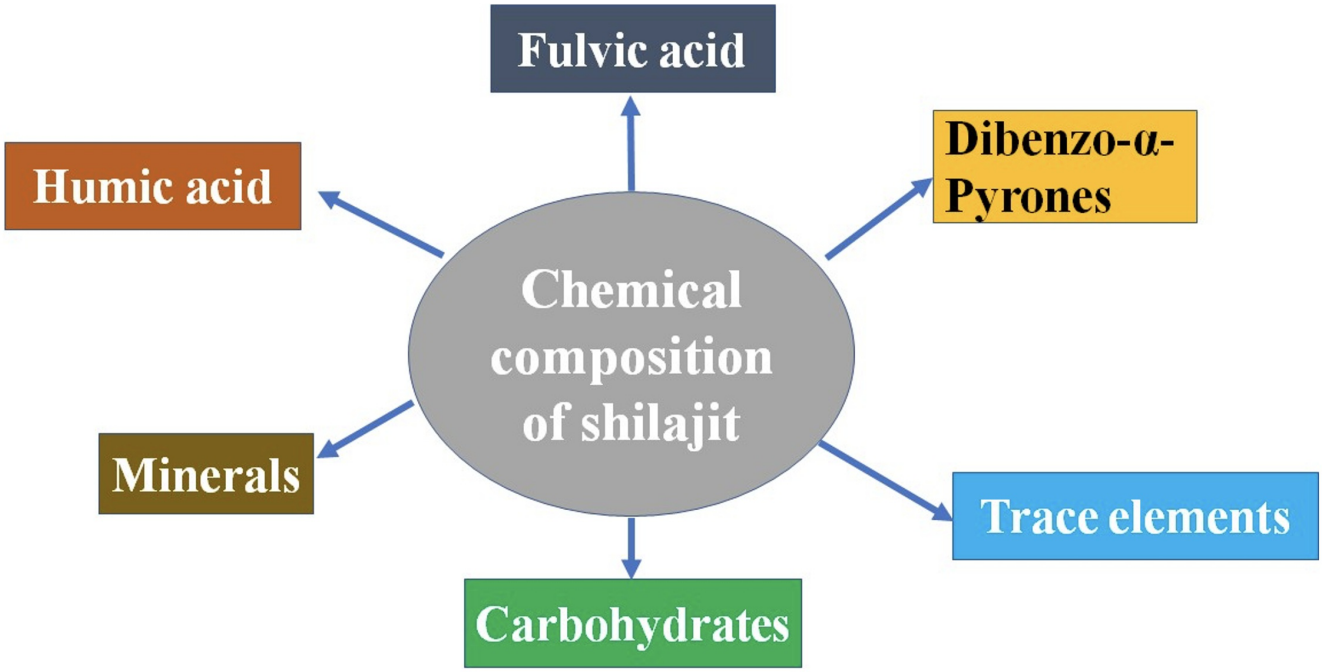

Figure 1. Major Phytochemical constituent present in the shilajit

Table 2. Major chemical constituents present in shilajit and their pharmacological activities

Composition	Pharmacological Activity	Reference
Fulvic acid	Antioxidant activity, Anti-inflammatory effects, Neuro-protective properties, Immunomodulatory effects	[33][34][35][36]
Humic acid	Antioxidant and free radical scavenging properties, Gastrointestinal protective effects, Anti-inflammatory and analgesic properties	[37][38][39]
Amino acid	Building blocks for protein synthesis, Involved in various metabolic processes	[40][41]
Dibenzo-Alpha-Pyrones	Adaptogenic properties	[42]
Trace Elements	Selenium: Antioxidant & anti-inflammatory effect Strontium: Bone health & potential anti-inflammatory effects Rubidium: Cardiovascular and potential anti-inflammatory effects	[3][43][44]
Minerals	Iron: Hematopoietic and oxygen-carrying properties Zinc: Immunomodulatory effects and wound healing Magnesium: Neuromuscular and cardiovascular support	[43][45][46]
Carbohydrate	Energy Source	[47]

Although it has been demonstrated that shilajit samples from various locations have differing organic compositions, they normally include 80-85% humic substances (such as fulvic acids, humins, and humic acids) and 10-15% non-humic chemicals. Overall, the composition of shilajit samples would include 14-20% humidity, 18-20% various minerals, 13-17% proteins (inclusive of a broad spectrum of amino acids), 18-20% nitrogen-free substances, 4-4.5% lipids, 3.3-6.5% steroids, 1.5-2% carbohydrates, and 0.05-0.08% alkaloids [48][49]. In the 1980s, extensive research uncovered the fundamental components of this material. These consisted of resin, triterpenes, sterol, amino acids, 3,4-benzocoumarins, aromatic carboxylic acid, and phenolic lipids; humus made about 60-80% of the mixture [50]. Organic matter is mostly composed of humic and non-humic molecules. All substances falling into one of the specific compound groups, such as carbohydrates, lipids, and amino acids, are categorized as non-humic substances [51]. Fulvic acid (Avg. mol. wt. 1200) has a lighter yellowish tint and a larger concentration of carboxylic groups compared to humic acid [52]. Humic acid, with an average molecular weight of 6500, is coloured between dark brown and black. Greater pH values cause it to dissolve, whereas acidic solutions cause it to become insoluble [53]. Fulvic acid is the bioactive component of shilajit, which is recognized to have immunomodulatory and hallucinogenic effects. Typically, a humic substance is composed of this bioactive ingredient [54]. Shilajit formulations also contain phenolic lipids, polyphenols, amino acids, gums, sterols, albumins, latex, triterpenes, and aromatic carboxylic acids, among other substances [55][56][57]. Its molecular makeup does undoubtedly differ by location. Recent studies using Size exclusion-high-performance liquid (HP-SEC) demonstrate that shilajit has particular molecular species of lignin's and polysaccharides [58]. All shilajit formulas contain humins, fulvic acids, and humic acids as humic components. The latter two are dibenzo-α-pyrones, which operate as transporters of other chemicals, and fulvic acids, the molecule that is physiologically active [56]. The charaka Samhita describes many types of Shilajit, including sarvana (gold Shilajit), lauha (iron shilajit), tamra (copper shilajit) and rajat (silver shilajit) [56][59]. Research has shown that the benefits of shilajit for health differ depending on where it was grown [56][60]. Shilajit smells

like urine and has a flavour that is a little bit pungent, astringent, bitter, and salty. The purified substance responds acidic ally to water and is nearly completely soluble in it. Gums, sterols, albumins, latex, triterpenes, and aromatic. The name "maharasa" designates a class of medicinal plants. A staple of the ancient Hindu Materia medica, shilajit is a drug that Hindu doctors use extensively to cure a range of disease. Conditions for which it is reported to be beneficial include phithisis, leprosy, diabetes, digestive diseases, erectile dysfunction and chronic bronchitis, dropsy, neurological disorders, and bone fractures [56]. Shilajit is a light brown to dark brown exudate with varying stability, is founded between 1000 and 5000 meters above sea level in sedimentary rocks of various strata all over the world [61].

Pharmacological Activities

Shilajit, an ancient traditional medicine utilized for treating a variety of diseases, has been connected to several biological processes. For thousands of years, it has been utilized as an adaptogen and rejuvenator. Multiple therapeutic properties have been confirmed by recent scientific researchers and some important pharmacological activities listed in Table 3 and Figure 2.

Table 3. Summary of pharmacological activities of shilajit

Pharmacological Activities	Mode of action	References
Adaptogenic properties	Helps regulate the production of stress hormones, supporting the body's ability to adapt to stress	[62]
Antioxidant activity	Prevents oxidative damage to cells and tissues by acting as a scavenger of free radicals.	[48]
Anti-inflammatory activity	Decreases the production of prostaglandins, which are known to induce inflammation, and inhibits the expression of COX-2.	[22]
Anti-diabetic effects	Preserves pancreatic beta cells, increases insulin sensitivity, and modifies glucose metabolism.	[63]
Anti-aging	Shilajit increases the life of cells by boosting mitochondrial function, lowering oxidative stress, and activating genes linked to cellular repair and longevity.	[43]

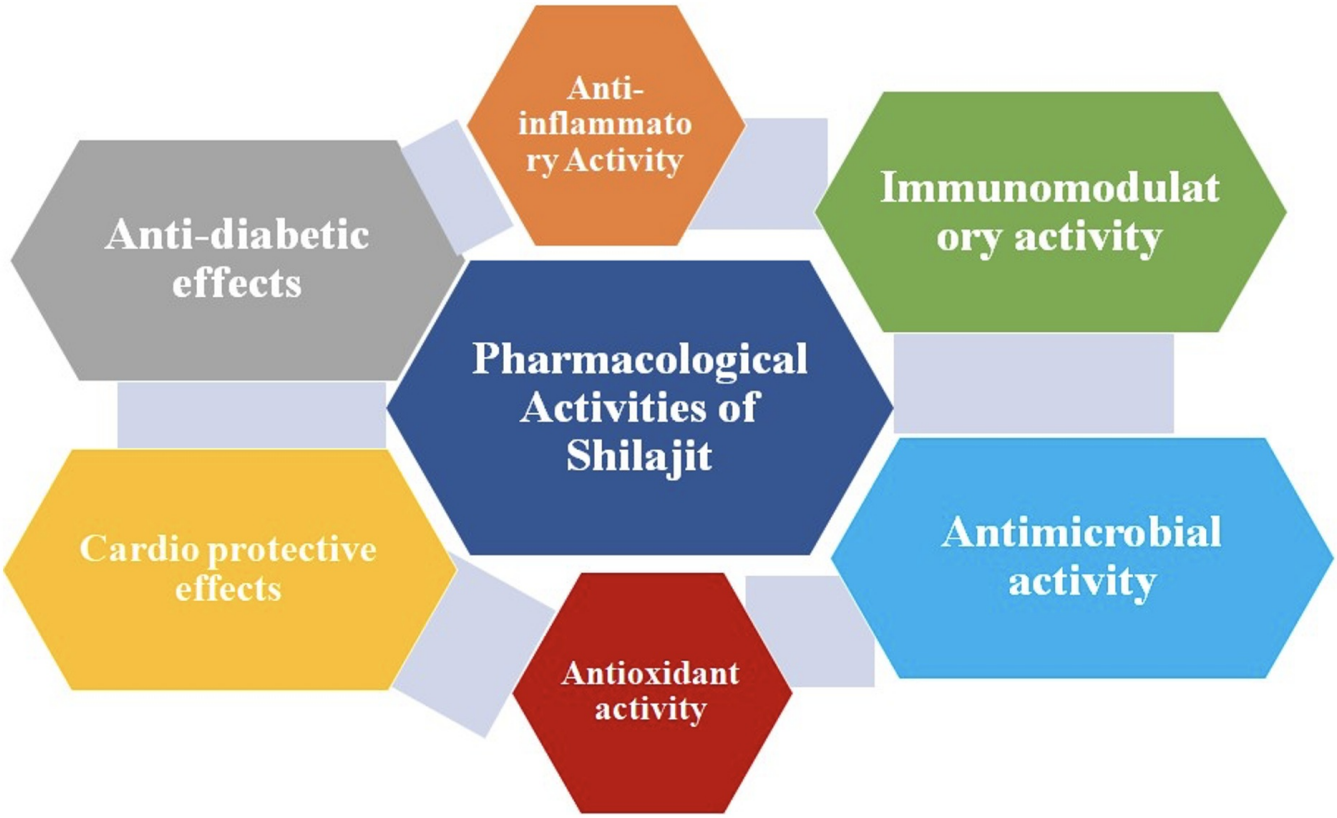

Figure 2. Pharmacological proprieties of Shilajit

Immuno-modulatory activity: Fulvic acid, the primary component of shilajit, has positive effects on immuno-modulatory activity. Extracting fulvic acid from Shilajit improved nitric oxide and reactive oxygen species (ROS) production in mice peritoneal macrophages. The uptake of [3H] thymidine in mouse spleen cells treated with FA1 increased in a dose-dependent manner. [64]. A dosage of 0.5 g/kg given to individuals with acute radiation illness between the first and the twentieth day following radiation therapy (180-220 r/min, dose 600r) has been shown to enhance lymphopoietic erythropoiesis. This is supported by a quicker recovery of lymphocyte counts in the spleen, bone marrow, and peripheral blood [65]. It was shown that pure shilajit caused T-cell-mediated cytotoxicity and enhanced the lytic potential of activated lymphocytes [66]. Shilajit has an effect on WBC activity that is positive, dosage dependent, and positively correlated with exposure duration [67]. It is believed that shilajit immunomodulatory qualities enhance the immune system's ability to combat bacterial infections [68][69].

Antimicrobial activity: In a research conducted in vitro, shilajit prevented the development of both kinds of bacteria, including ones that may cause human illnesses, demonstrating potentially good anti-microbial activity [70]. In vitro, shilajit extraction at various ratios inhibited S aureus but had no impact on E coli [71]. Similar to prior research, shilajit extract had good efficacy against several microorganisms. The most affected organisms were E. coli [72]. Exposed to UV light All known bacterial strains were resistant to Shilajit antifungal effect, however it may have had considerable antibacterial activity against Penicillium chrysogenum [73]. Shilajit supplementation at a level of 2g/kg or 4g/kg has been shown in a study to enhance M. rosenbergii immunity, disease resistance, and antioxidant activity against A. hydrophila [74]. Whereas another research discovered that treatment for individuals with pulmonary tuberculosis was shortened when Shilajit was

administered [75]. A different study found that shilajit effectively inhibits E. Coli bacteria. This finding may be connected to the fulvic and benzoic acidic components found in shilajit. [76].

Anti-diabetic effects: According to an animal study, the daily treatment of 100 mg/kg of Shilajit has been shown to reduce the hyperglycaemic reaction to streptozotocin starting on day 14 of continuous and consistent dosing [77]. In an additional investigation, it was noted that shilajit 100 mg/kg/day in conjunction with conventional medications may improve blood sugar regulation [78]. It was shown that Shilajit, OS, significantly improved PP measurements of blood sugar ($P<0.001$) and fasting measurements of blood sugar level ($P<0.001$) in clinical research involving a group of people with diabetes mellitus [79]. Shilajit has 10-12 mg/100g of 1,2-dithiolane, 3-pentanoic acid, and ȧ-lipoic acid. According to a study, lipoic acid has demonstrated good efficacy in the management of type-II diabetes [80].

Antioxidant activity: Fulvic acid and dibenzo-α-pyrones that give shilajit extract its antioxidant properties[81].In research, the aqueous extract of shilajit shown a value of 11.9 µg/mL for DPPH radical scavenging [82]. In rat liver homogenate, oxidative stress induced by CCL4 was employed to assess Shilajit's capacity to scavenge free radicals. Lipid peroxidation, a measure of oxidative stress, was chosen as the study's parameter. According to this study, shilajit increases the activity of antioxidants in the bodies of rats [3]. To evaluate the antioxidant effects of*Asphaltum punjabinum*, the capacity of several sample solutions to inhibit lipid peroxidation produced by iron (Fe2+) in rat liver homogenates was measured [83]. Shilajatu provided methyl methacrylate (MMA) with complete protection against hydroxyl radical-induced polymerization and served in the reversible no-captodative agent [84]. The native Shilajit from the Aseman Mountains of Bahr shown a moderate level of antioxidant capacity, [85] Similar studies on Shilajit from Pakistan and Afghanistan demonstrate a potent antioxidant activity [86].

Anti-viral property: In a clinical study, shilajit was demonstrated to enhance ART results and lessen HIV's recurrent resistance to treatment [87]. Shilajit and officinalis together exhibited a strong potential for HIV virus viral enzyme inhibition in an in vitro investigation [88]. Shilajit possesses a dose-dependent inhibitory activity in opposition to the infectivity of HSV1, HSV2, HCMV, and RSV (EC50 values: correspondingly, 31.08µg/ml, 12.85µg/ml, 34.54µg/ml, and 30.35µg/ml), however it is inert against HRV and VSV2 [89]. Another in-vitro investigation has demonstrated the effectiveness of Fulvic acids from Shilajit extract protect against influenza and other viruses [90].

Cardioprotective effects: In an animal experiment including the injection of 85 mg/kg-1 of isoproterenol to cause myocardial damage, it was shown that shilajatu preserved the maximum ±dp/dt, decreased the concentration of serum cardiac troponin and reduced the level of heart damage [91]. Shilajit has been demonstrated to have positive effects on improving endothelium function in a double-blind placebo-controlled study where 50% of the participants were consume two capsules twice daily with 250 mg of Shilajit or a placebo for a duration of 12 weeks. [92]. Shilajit is more advantageous than simvastatin for lipid profile, according to another study conducted on animals [93]. In other animal investigation has certified Shilajit beneficial effects on controlling lipid profiles [94]. Shilajit increased the amount of antioxidant enzymes in the heart, conserved the heart's histoarchitecture, and enhanced cardiac function when isoproterenol was administered, according to experimental findings from another research, Conclusion: The cardiotoxic impact of ISO in rat heart can be reduced by shilajit at a dosage of 500 mg/kg [95].

Anti-Ulcerogenic and inflammatory effects: Shilajit has reduced the stomach ulcer index and raised the carb/protein ratio, all of which point to an enhanced mucus barrier. In rats suffering from adjuvant-induced arthritis, granuloma pouch, and acute carrageenan-induced pedal edema, a strong anti-inflammatory activity of shilajit was discovered. [96]. Another clinical study, two groups received normal saline along with wound treatment, while a third group received water containing a 20% concentration of Shilajit. The intervention group's noticeable wound healing was observed [97]. The processed Shilajit may be very helpful in treating related inflammatory diseases and wound healing as long as it is taken in accordance with a well-considered dosage regimen [98]. Fulvic acids have been demonstrated in a study to decrease the occurrence of duodenal ulcers in an animal model when combined with 4′-methoxy-6′ carbomethoxy biphenyl [99]. It was additionally shown that shilajit had strong anti-inflammatory effects the three models of acute, subacute, and chronic-inflammation. Shilajit, at a 50 mg/kg dose, was shown to substantially decrease carrageenan induced hind paw oedema in rats, with an outcome similar to that of betamethasone (0.25mg/kg) and phenylbutazone (100mg/kg, intraperitoneal) [34].

Effects on infertility and testosterone: In comparison to a placebo, a study revealed that taking pure Shilajit for ninety days markedly raised free testosterone and dehydr-oepiandrosterone (DHEAS). Gonadotropic hormone levels are maintained within normal limits [100]. Shilajit treatment has been shown to considerably enhance the physical and mental rejuvenating effects of mature Lohi rams in an animal investigation [101]. Shilajit is also used employed in the treatment of male sexual dysfunction and has been described as a powerful aphrodisiac. It has been documented that in rats and humans, Shilajit elevates blood testosterone levels and sperm counts [10][102][103]. According to the available material, no instances of negative effects have been reported over the course of research including both humans and animals [104].

Anabolic activities: According to the results of the trials, administering Shilajatu extract (0.5 gm/kg per oz, every day for ten days) accelerated the process by which the liver produces energy, improved the transport of mineral particularly phosphorus, magnesium and calcium to the tissues of muscles bones and muscles, and accelerated the synthesis of proteins and nucleic acids [105]. Shilajit administered 500mg as a dose every day has produced advantageous adoption of muscle and connective tissue [106].

Anti-AIDS activity: Shilajit possesses the ability to both redistribute viral burden and stimulate the immune system [7][85][107]. In a multi-component natural product combination that was utilized in clinical trials on AIDS patients, shilajit was one of the key ingredients. Three necessary and three auxiliary ingredients were included in the product's composition. 22 out of 36 patients who were included showed positive signs of recovery following a six-month course of formulation-based treatment. Their CD8 and CD4 cell counts rose from 733 ± 483 (CD8) and 259 ± 119 (CD4) to 356 ± 203 and 984 ± 356, respectively. A significant symptoms relief and an increase in CD4, 516±272; and CD8 1157±428 counts of cell were seen in ten individuals who had therapy for a year [97]. In a study shown that, Humic materials can be used in clinical practice to develop anti-HIV microbicide formulations, improving HIV-1 prevention efficacy. These materials, easily produced from coal or peloids, can be used in resource-limited settings like South Africa, particularly during the AIDS pandemic [108].

Combinational approaches

Medicinal plants combination frequently shows better results than single drugs for treating illnesses. The theory of drug combinations is firmly established in conventional medicines, and significant advancements have been accomplished throughout time. Previously in the past, Patients with infectious illnesses and cancer now have new hope through medication combination therapy [109]. The most often used herbal remedies in toxicological situations, despite the fact that the causes are yet unclear. In order to prevent toxicity, it is well recognized that heavy metals of any kind cannot be included in medicinal formulations. But a large number of Ayurvedic combined herbal formulation tracks the principles of Rasashastra, it includes using metals for their medicinal qualities to generate Rasausadhies (Herbo-Mineral Metal Preparations). Improved palatability, extended shelf life, tastelessness, quick action, and reduced dose are allegedly intrinsic characteristics of these products [110].

In the traditional Indian medicinal system, there is a preference for plant formulations and blended extracts over single plant extracts. It's frequently referred to as Ayurvedic herbal treatments are prepared in many dose forms, with poly herbal formulation being the majority [111][112]. Studies indicate that there can be possible interactions between naturally occurring plant components and traditional herbal formulations. Among these are reciprocal guidance, reciprocal assistance, reciprocal discipline, and reciprocal [111]. The extraordinary therapeutic efficacy of the formulations in the Unani medical system is contributing to their increasing adoption on a global scale. Legislation and regulatory development have therefore been slowed down by the absence of assessment [112]. The research revealed that many individual plants contained significant quantities of flavonoids and phenolics. When these components were combined with green tea in a polyherbal blend, the resulting extracts exhibited the highest levels of antioxidant activity [112]. In most conventional systems, a combination of herbs compared to a single herb is preferable for managing diabetes due to its synergistic effects and less adverse effects [113]. It has been demonstrated that diabetic wound cream with a polyherbal composition is equally secure and efficient for managing diabetic foot ulcers as standard silver sulphadiazine cream [114]. Herb-herb formulations have been used by traditional herbal treatment systems in several regions of the world because of their complex pharmacological properties [115]. Combinations of botanicals are used in Ayurvedic and herbal therapeutic preparations; each of them includes a type of chemical components that, when combined, may provide the intended outcome. Ayurvedic products are seeing rapid growth in the market due to rising interest in using plant-based formulations [116]. There are two ways that synergism functions depending on the type of interaction (i.e., Pharmacokinetics and pharmacodynamics) [117]. Herbal remedies are widely used and, against the assumption that they are harmless, they are frequently combined and derived from plant sources that vary widely in terms of species, growth environments, and physiologically active ingredients. The presence of several active components in botanicals, and their combined use may have a potentiating impact that cannot be achieved with just one component, the ability to combine different components is a key potential advantage over traditional single-component medications. Plant-based pharmacological compounds included in polyherbal formulations may have synergistic, potentiative, agonistic, antagonistic effects due to the numerous active principles they are connected with [118]. Plant combinations that include these components may be more active than the individual extract. On the other hand, a high component count may also result in chemical incompatibility, which may bring instability [119]. Whereas the drugs and cosmetic act was established to

regulate Management of production and quality assurance, the regulation of Ayurvedic herbal preparation manufacturing is relatively laxer in India, where the majority of Ayurvedic's polyherbal formulations are created and exported [111]. According to the good clinical practices, toxicity studies and clinical trials on herbal formulations are not mandatory for application of patents and grant of manufacturing licenses to the Ayurvedic herbal formulation manufacturer [120].

Understanding Herb-Herb Interactions: Plant extract combinations or the combination of multiple of their active ingredients can have synergistic effects [121]. According to Berenbaum (1989), these synergy effects are not just additive effects but also a real synergism. As a result, there should be a decrease in adverse reactions in addition to improved efficacy at lower doses of the individual components [122]. Combining molecular, cellular, and analytical methods may help better investigate and characterize the effects of multi-item prescriptions [123]. To understand and support the empirical results, their exact pharmacological effects must be determined. However, it is improbable that conventional pharmacological methods would adequately elucidate the distinct combined impact of a blend of herbs. "Omic" technology and systems biology might provide a fresh angle for evaluating the combinational effects of Phyto-pharmaceuticals [122].The term "herbomics" was created by Sarris et al. to refer to the "omic" studies of herbs and highlight the significance of systems biology in herbal research [124]. Small amounts of certain active phytochemicals that target multiple targets linked to Perhaps a disease complex will work better and secure than high doses of a chemical therapy that concentrates on important area. The common components of phytomedicines, standardized extracts, fractions, or polyherbal mixtures, are helpful because of this. Compared to traditional, all-chemical therapies, phytomedicines are simpler to make [125].

Benefits of combination approaches of herbal medicine:[126].

- Indeed, the presence of multiple components in a combination acts to augment the effectiveness of one drug by another. When the individual components are employed in isolation, attaining this heightened activity may not be achievable.
- Certainly, formulations that include multiple herbs commonly display a wide therapeutic window. They prove effective at lower doses and remain safe at higher doses, with a considerable number showcasing a favourable risk-to-benefit ratio.
- Mixtures of herbs containing diverse ingredients act on multiple targets simultaneously, offering comprehensive relief. The presence of various types of ingredients addresses the condition through different mechanisms, providing a well-rounded remedy for a specific problem.
- Pharmacokinetic or pharmacodynamic synergism can be achieved through the combined action of two herbs. Pharmacokinetic synergism occurs when two herbs work together to enhance each other's distribution, metabolism, excretion, and absorption. On the other hand, pharmaceutical synergism involves targeting active principles from multiple components toward shared physiological systems, potentially resulting in synergistic effects.
- To achieve the required pharmacological activity, herbal combinations may be administered at lower dosages. This approach, compared to allopathic medicine, reduces the likelihood of adverse side effects.
- A holistic approach that takes into account multiple aspects of a health condition, seeks to minimize potential side

effects by employing lower doses of individual herbs. It includes balancing properties for a harmonious effect, utilizes adaptive effects to boost stress resilience, customizes the approach to address specific health concerns, relies on traditional wisdom, and improves bioavailability through interactions.

Nano formulations

Nanotechnology is linked to systems and materials that, owing to their nano-scale dimensions, display unique, significantly improved chemical, physical, and biological properties, processes, and phenomena. Nanotechnology is defined by the dictionary as "the design, characterization, manufacture, and shape and size-controlled application of materials in the nanoscale" [127].It is defined as the process of working with material at the atomic and molecular sizes, or between 1 and 100 nm [128]. Any technology that operates at the nanoscale and has uses, such using individual atoms and molecules to create useful structures, is referred to as nanotechnology [129]. Absolutely! The advancement of novel products, upgrading outdated manufacturing equipment, and reformulating special materials and chemicals for improved performance can all benefit significantly from nanotechnology. This approach holds the potential to reduce the demand for energy and materials, minimize environmental harm, and facilitate environmental remediation. While the conservation of energy and materials is advantageous for the environment, nanotechnology introduces an exciting prospect of discovering more environmentally friendly solutions to challenges. The application of nanotechnology in the environment not only addresses potential difficulties related to nanotechnology but also offers solutions for existing environmental issues and problems arising from the interactions of materials and energy with the environment [130]. Nano systems based on nanotechnology exhibit potential in mitigating side effects owing to their elevated biocompatibility, facile surface functionalization, capability to target malignancies, and proficiency in drug delivery [131]. Recently, there have been a worldwide surge in interest in nanotechnology due to its diverse applications across various fields. These include catalysis, drug delivery, the chemical industry, biological sciences, optoelectronics, mechanics, and space industries [132].The application of nanostructures and nanophases across various scientific fields has illustrated how nanotechnology can serve as a bridge between the biological and physical sciences [133].The field of delivery systems has made significant advancements in recent years, allowing for the targeted administration of therapeutic agents or active natural substances to specific areas for the treatment of various illnesses [134][135].The use of naturally occurring bioactive compounds in combination with nanoscience is highly desirable and has been growing rapidly in the past several years. It has a number of advantages in terms of delivering natural materials for the management of several ailments, including cancer. Organic substances have been extensively investigations in the therapy of ailments due to their unique activities, which include tumour-suppressive autophagy and antimicrobial activity [136].

Polyphenols act as the principal constituents in numerous nutraceuticals, demonstrating attributes such as metal chelation and anti-inflammatory effects. Nutraceutical’s and specific bioactive components like Andean Shilajit, collected gathered from Chile's northern Andes, have received scientific validation. Andean Shilajit is a material that has undergone fossilization over millions of years through the action of various microbiological organisms breaking down plant matter. It is rich in inorganic substances like magnesium, selenium, and other minerals, along with humins such as fulvic and humic

acids [137][138][139].

Andrade V et al,[140] prepared the interest in treating Alzheimer's disease has led to a focus on emerging bioactive compounds like Andean Shilajit and scientifically proven nutraceuticals. BrainUp-10®, an advanced formulation that includes AnSh and is enhanced with a B vitamin complex, has shown effectiveness in managing the condition. Future research efforts will center on exploring its molecular underpinnings. Absolutely, Andean Shilajit and its components can influence neuronal activity, leading to neurogenic effects that impact the number and length of processes. Crucially, they don't compromise the viability of cells. Furthermore, they demonstrate the capability to facilitate the disintegration of tau protein oligomers and tangles, suggesting their potential for the treatment of neurodegenerative conditions such as Alzheimer's disease. Two promising treatment options emerged after the molecular characterization of fractions. To elucidate the molecular mechanisms behind these effects, these candidates will be the focus of future investigations using state-of-the-art experimental methods. In conclusion, this will encourage additional research into the safety and effectiveness of natural remedies in the onset and/or progression of neurodegenerative and neuro developmental diseases.

Perumal P, et al,[141], Shilajit, a neuroprotective agent, interacts positively with other drugs. Research aims to combine shilajit based ZnO nanoparticles and screen their effects on cervical cancer cell lines, using shilajit extract as a reducing and stabilizing agent. Shilajit extract-derived ZnO nanoparticles show promising anticancer properties, highlighting the potential of natural remedies as substitutes for pharmaceuticals. Further investigation is needed to ascertain the precise mode of action against cervical cancer, enabling the development of this novel ZnO nano-formulation.

Alshubaily et al. 2022 [142], investigated the anti-osteoporotic effects of Shilajit-loaded chitosan nanoparticles in a study involving rats with glucocorticoid-induced osteoporosis. The main experimental groups included Nano chitosan and nano chitosan combined with shilajit water extract. The results demonstrated the effectiveness of nano chitosan and nano chitosan combined with shilajit water extract in levels of calcium, osteocalcin, calcitonin and phosphorus. Furthermore, it proved effective in decreasing hydrogen peroxide levels, thereby preserving antioxidant levels. As a result, Nano chitosanand nano chitosan combined with shilajit water extract may contribute to the enhancement of biomarkers for bone growth and the reduction of oxidative stress.

Future scope

In the last five decades, nanotechnology has rapidly progressed and has become the cornerstone for a diverse array of noteworthy commercial applications. Particularly within the pharmaceutical field, nanotechnology has exerted a major impact on healthcare technology, including medication delivery methods, imaging probes, and diagnostic biosensors [143].The utilization of nanomaterials in the food and cosmetics industries has witnessed a substantial increase, aiming to enhance production processes, packaging efficiency, shelf life, and bioavailability [144].Certainly! To ensure the safety and sustainability of nanotechnology, it is crucial to possess the ability to evaluate and address potential hazards. For "nano" to genuinely play a role in fostering a future and earth sustainably, this becomes indispensable. In

essence, despite the capacity of nanotechnologies to potentially reduce the probability of going over any of the nine planetary borders- For instance, freshwater consumption, biogeochemical fluxes, ocean acidification, atmospheric aerosol pollution, stratospheric ozone depletion, climate change, biosphere integrity, and the release of new chemicals—effective risk assessment and mitigation are paramount [145]. Nanoparticles are being utilized as food sensors to assess the safety and quality of food, primarily due to their antibacterial properties against food-borne pathogens [144]. Nanotoxicology and nanomedicine are two new scientific areas that have evolved as a result of these concerns. Nanotoxicology is the study of potential negative health effects of nanoparticles on humans [146].The concept of nanorobots and nanodevices with the capability to diagnose and heal tissues, along with complete external control mechanisms, has indeed sparked significant excitement [147].

Conclusion

The following article gives a summary of the primary characteristics, uses, pharmacology, phytochemicals, and medicinal importance of *Asphaltum punjabium*. In this compilation, you'll find the most well-known and established pharmacognostic investigations, offering comprehensive details on both pharmacological and phytochemical analyses, with a specific emphasis on their therapeutic benefits. Shilajit contains a variety of advantageous elements such as minerals, vitamins, plant metabolites, fulvic acid, humic acid, trace elements, and carbohydrates. The combined presence of these components enhances the medicinal qualities of shilajit, positioning it as a valuable herbal solution. These plant-derived chemicals have been linked to various pharmacological functions, such as immune system regulation, antiviral properties, antioxidative advantages, and reducing inflammation etc. This review will be crucial for individuals engaged in the investigation of shilajit, and the exploration of its combination with herbs will assist researchers in effectively utilizing nano formulations. Moreover, it might offer an opportunity for the food and nutraceutical sectors to develop more potent bioactive functional health products.

Statements and Declarations

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Conflict of interest

The authors declare no conflict of interest.

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