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Research Overview

Medical Drugs From Humus Matter: Focus on Mumie

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Strategy, Management and Health Policy				
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ABSTRACT In this review, we focus on the medicinal drugs from humus matter such as peat, sapropel, and mumie. The most clinically available medicines, containing peat and sapropel extracts, are Torfot, Tolpa Peat Preparation (TPP), Peloidodistillate, Humisol, Peloidin, FiBS, and Eplir. Much attention in the review is concentrated on mumie composition, its pharmacological properties, and new pharmacological drugs with mumie (Shilagen, Abana, Cystone, Diabecon 400, EveCare, Geriforte, Lukol, Pilex, Rumalava, Tentex forte, Nefrotec, Adrenotone, Siotone, La-Tone Gold, Andro-Surge, Solanova Libidoplex). It was concluded that therapeutic properties of crude extracts from peat, sapropel, and mumie have similarity to the ones of fulvic and humic acids. They are antibacterial, antitoxic, antiradical, antiulcerogenic, antiarthritic, immunomodulatory, and antiinflammatory properties. Possible directions for better development of new drugs from humus matter are discussed. Drug Dev. Res. 57:140–159, 2002.

Key words: plant humification; peat; sapropel; mumie; shilajit

PEAT, SAPROPEL, AND MUMIE AS HUMUS MATTER

In the last three decades, focus on research of humus matters has increased all over the world, and a large body of evidence has collected to show immense potential of peat, sapropel, and mumie used for developing new medicinal drugs.

Humus matter consists of organic residues that have lost their original structure after decomposition in the environment [Stevenson, 1994]. In contrast to the living cell, where the synthesis of biopolymers is achieved in accordance with the genetic code, in the process of humification there is no established program of any kind; therefore, any substances can appear, both simpler and more complex than initial biomolecules. The resultant products again undergo the synthesis reactions or decomposition, and this process continues practically continuously. As a result of numerous reactions in the humus matter, only the most stable compounds are accumulated, which exist longer than more labile substances [Orlov, 1997]. Examples of biogenic sediments formed mainly of plants include peat, sapropel, and mumie.

Peat is organic soil formed as a result of incomplete disintegration and humification of died marsh plants in conditions of high humidity. The organic matter of peat in 90% consists of humin, humic and fulvic acids (up to 40%), lignin, polysaccharides, lipids, pectines, hemicellulose, and cellulose [Orlov, 1995; Mathur et al., 1993].

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Sapropels are silted deposits of water reservoirs (lakes, peat marshes, sea estuaries) and contain a large quantity (>50%) of organic matter (lignin–humus complex, carbohydrates, bitumen, etc.) in colloidal state. The organic components of "mature" sapropel are produced by the slow decomposition and humification of plants and phytozooplankton in anaerobic conditions [Rohling, 1994]. This process is accompanied by the condensation of phenolcarboxylic acids with formation of new high-molecular organic compounds such as humic and fulvic acids. Peat and sapropel are used in pelotherapy as external remedies. The internal application of extracts from peat and sapropel became usual in Russia and Poland in connection with pioneer works of academician V. P. Filatov, who developed the theory of biogenic stimulators about 70 years ago [Filatov, 1961].

Mumie (common names: shilajit, mummiyo, asphaltum, vegetable asphalt, mineral pitch) is a semihard, brownish black to dark, greasy, black resin that has a distinctive coniferous smell and bitter taste. Mumie is found in mountain regions of Afghanistan, Bhutan, China, Nepal, Pakistan, Tibet, and some regions of the former USSR (Ural, Baykal, Sayan, Caucasus, Altai mountain regions, Kirgysia, Tajikistan, Uzbekistan, and Kazakhstan), where it is gathered in small quantities from steep rock faces at altitudes between 1 and 5 km [Khakimov, 1974; Ghosal et al., 1991b]. On the basis of special features of origin, mumie is divided into three types: petroleum mumie, plant mumie (mumie-asil), and mumie-kiem [Khakimov, 1974]. It is assumed that petroleum mumie is a result of transformation of deep petroleum products of mountains. Mumie-kiem is formed as a result of the long-term humification of guano (feces) of alpine rodents, in particular rock vole *Alticola strelzowi*. Mumie-asil is formed due to the long-term humification of *Euphorbia* and *Trifolium* (clover) plants and lichen [Ghosal et al., 1976, 1988; Korago, 1992]. In fact, radioisotope analysis of mumie was shown that samples from Altai have an age between 500 and 1,500 years, and the age of Central-Asian samples is up to 15,000 years. Mumie-asil has the highest therapeutic quality, and it is this type of mumie and its aqueous extract that are under discussion in the review.

MEDICAL DRUGS FROM PEAT

The humification process leads to change in pharmacological properties of peat extracts, in particular, to enhance in antiulcerogenic and antiradical activity of peat extracts [Yudina et al., 1998a, 1998b]. For some peat humates, the antitoxic properties are also characteristic [Lotosh, 1991]. Pharmacological properties of peat extracts are studied mainly on such patented drugs as Torfot (Russia) and Tolpa Peat Preparation (TPP) (Poland). The chemical composition of these preparations is standardized, which makes it possible to conduct systematic studies on the influence of peat extracts on biological systems.

Torfot

Torfot is a product of distillation of specific peat layers. As a medicinal drug, it is a sterile liquid with the characteristic smell of peat. Torfot is administered in the form of hypodermic or subconjunctival injections in ophthalmology for treatment of patients with keratitis, chorioretinitis, and vascular and degenerative processes in the retina [Bushmich and Golatska, 1972; Gorgiladze et al., 1984; Shpak et al., 1990]. Torfot possesses antibacterial and antiinflammatory action, and improves blood circulation and tissue regeneration. These properties of the drug are the reason for its application in stomatology [Dunaev et al., 1996]. It was shown that Torfot is also applicable for complex treatment for other chronic inflammatory diseases and pulmonary tuberculosis [Strelis et al., 1991].

Tolpa Peat Preparation

TPP was first produced in the laboratory of Polish professor Stanislaw Tolpa (1901–1996), and now it is manufactured by Torf Corporation (Wroclaw, Poland) on the base of peat extract obtained from selected peat deposits in ecologically clean and unpolluted areas in Poland. TPP contains organic substances, primarily bound sugars, amino acids, uronic and humic acids, and mineral salts. TPP (as tablets and gels) is a natural drug registered in Poland for medicinal use. No embryotoxic or teratogenic effects were observed in hamsters or rats after the administration of TPP in daily doses from 5 to 50 mg/kg [Juszkiewicz, 1993]. TPP was found to be neither mutagenic nor genotoxic in selected short-term tests [Koziorowska et al., 1993], and was unable to induce or enhance an allergic sensitization in mice and guinea pigs [Maslinski et al., 1993]. The cytotoxicity (CD50) of TPP for human peripheral blood leukocytes is 1–9 mg/ml (in vitro test) [Inglot et al., 1993].

TPP is an interferon-α and -γ and tumor necrosis factor-α (TNF-α) inducer in cultures of human peripheral blood leukocytes. The optimal concentration of TPP for cytokine response in leukocyte culture was 10–100 μg/ml [Inglot et al., 1993]. TPP (10 and 100 μg/ml) also enhanced the interferon-β and TNF-α production by mouse peritoneal macrophages [Blach-Olszewska et al., 1993]. The promoting effect of TPP (one intraperitoneal injection a day for 4 days) on mouse humoral response occurred for doses of 0.5–10 mg/kg, whereas the doses of 100 and 250 mg/kg had a suppressive effect. The impact of TPP on the

percentage of splenocytes forming E-rosettes was also dose dependent, but in this case stimulating activity was observed for the doses of 2.5–25 mg/kg [Obminska-Domoradzka et al., 1993b]. The intravenous administration of TPP to rabbits at a dose of 5 mg/kg increases the percentage of phagocytizing cells and phagocytic activity of neutrophils. A single administration of TPP (50 mg/kg) to rabbits with lipopolysaccharide (LPS)-induced fever leads to total inhibition of endotoxic shock syndrome [Obminska-Domoradzka et al., 1993a]. TPP increased the ability of human mononuclear leukocytes from patients with coronary artery disease to induce neovascularization in the local graft-versus-host reaction, and decreased the high activity of lymphocytes from rheumatoid arthritic patients [Skopinska-Rozewska et al., 1993]. The interleukin-1 release in cultures of mononuclear leukocytes from patients with rheumatoid arthritis was inhibited by TPP in concentration of 100 pg/ml [Skopinska-Rozewska, 1991]. Both TPP and its fractions suppress the lipid peroxidation in the mitochondria from human placenta [Piotrowska et al., 2000].

MEDICAL DRUGS FROM SAPROPELES

Sapropeles of different kinds are varied in their ability to correct hepatic function in rats with toxic hepatitis and have positive effect during experimental therapy of pancreatitis [Ioshchenko and Zyrianova, 1991; Kuzmenko et al., 1998]. The restoring influence of sapropeles appears to occur due to both their adaptogenic and antioxidant effects [Krylov et al., 1990; Nizkodubova et al., 1991; Yudina et al., 1998a]. At present, the medicinal remedies Humisol, Peloidin, and FiBS were produced from the different kinds of sea mud.

Peloidodistillate

Peloidodistillate is produced by distillation of sapropel from Tambukan lake (Caucasian region, Russia). The variety of this drug is "Vitapeloid" (1% solution of pyridoxine hydrochloride in Peloidodistillate). Therapeutic effect of the drug is caused by the presence of phenolcarboxylic acids, amines, vitamins, and microelements in its composition. The preparations stimulate metabolic processes in organism, accelerate regeneration ability, increase the organism resistance to unfavorable factors, and activate immunity. The drug does not possess allergic, teratogenic, and carcinogenic properties. It is applied in ophthalmology for treating patients for degenerate processes of cornea and retina, and initial forms of optical nerve atrophy [Degtiarenko et al., 1989]. The drug is also recommended against radiculites and neuralgias. In gynecology it is used against chronic inflammatory processes.

Humisol

Humisol (produced in Tallinn, Estonia) is 0.01% solution of humic acid fractions from Haapsalu (Baltic Sea) estuarine mud in 0.9% NaCl solution. Humisol is used (intramuscularly or via electrophoresis) in the cases of chronic radiculites, plexitises, neuralgia, rheumatoid arthritis, arthroses, chronic diseases of tympanum, paranasal sinuses, rhinitis, and other diseases for stimulation of immunity. For the patients treated with Humisol as adjuvant drug, the salmonellosis course was more favorable, the period required for recovery was shorter, and immunity indices earlier became normal [Vereshchagin and Golosnoi, 1994]. The antimutagenic effect of Humisol in cultures of blood T-lymphocytes exposed to cyclophosphane was discovered [Sevostianova, 1998].

Peloidin

Peloidin is a filtrate of specific kind of mud solution from Odessa (Black Sea) estuarine sapropel. Oral administration and electrophoresis of Peloidin are beneficial in lesions of gastric and duodenal mucosa [Komarova et al., 1991] and diseases of the gallbladder and biliary tract [Kuberger and Kalmanovskaia, 1966]. Peloidin phonophoresis proved to be valuable in the treatment for pathogenetic condition at all stages of lumbar osteochondrosis [Shmakova et al., 1990]. The drug is also applicable for treating patients with inflammatory processes of the genital system [Riabtseva et al., 1975].

Peloidin (with phonophoresis) and Humisol (as intramuscular injections) are demonstrated to cause a distinct increase of cellular immunity indices, and a positive trend in biochemical parameters and cardiovascular function in patients with pulmonary tuberculosis [Strelis et al., 1989, 1991; Strelis and Zhivotiagina, 1991].

FiBS

FiBS (abbreviation of author names: *Fi*latov VP, *B*iver VA, *S*korodinskaya VV) is a product obtained by distillation of specific kind of sea mud. It contains cinnamic acid and coumarins. FiBS possesses immunomodulating action on primary humoral immune response and does not increase a delayed-type hypersensitivity reaction [Degtiarenko et al., 1989, Degtiarenko, 1990].

Eplir

Eplir is a 1% oil solution of lipid fraction from specific sulfide mud. Eplir administration to rats

with CCl_4-induced hepatitis protects the liver parenchyma against dystrophy, necrosis, and inflammation [Vengerovskii et al., 2001]. The mechanism of Eplir biological action is determined by its antioxidant properties [Saratikov et al., 1990].

PHARMACOLOGICAL PROPERTIES OF MUMIE

Mumie is a complex natural mixture of organic (60–80%) and inorganic (20–40%) compounds and trace elements [Korago, 1992; Peerzada et al., 1999]. Mumie samples from different regions of the Earth have similar physical properties and qualitative chemical composition, but they differ in percent ratio of components. The levels of biologically active ingredients vary with geographic region, so some mumie samples may have high levels of the active ingredients. On dissolving in water, nearly 30–50% of the weight of mumie passes into the supernatant liquid, and the sediment includes mineral and plant residues in quantities depending on purity of the samples used.

Although mumie has been used in the folk medicine of different countries for almost 3,000 years, there are still many legends involving its mysterious origin. In Arabic countries mumie is called "mountain sweat"; in Burma, "mountain blood"; in Tibet and Mongolia, "rock juice"; and in Altai, "mountain oil." "Shilajit" in Sanskrit means "conqueror of mountains and destroyer of weakness." The name "mumie" was devised by the Arabs. Initially this medicine was called "Mum" in Persian. In ancient Egypt, this wonderful resin was used for embalming mummies.

Mumie was traditionally used in Asian herbal medicine both inwardly and outwardly against injuries, bone fractures, dislocations, diseases of skin, diseases of peripheral nervous system (neuralgia, radiculitis), and also as a soothing and antiinflammatory agent. Greek physicians used this medicine as an antidote to poisons and in the treatment of various problems including arthritis and inflammation. Avicenna in *Canon Medicinae* wrote that mumie possessed the ability to resorb tumors and pimples. "Mountain wax" in the form of drinking and rubbing is an excellent remedy for pains with dislocations and fractures, injuries, wounds, and paralysis of facial nerve. Mumie is useful in cases of migraine, vertigo, diseases of the ear, angina, hemorrhages, diseases of the gastrointestinal tract and urinary organs, and bites from snakes and scorpions [Rasulov, 1964]. Mumie was used as a rejuvenator in traditional Russian and Ayurveda medicine [Tiwari and Tiwari, 1973; Khakimov, 1974].

Mumie is prescribed for genitourinary diseases, diabetes, jaundice, adiposity, enlarged spleen, digestive disorders, epilepsy, nervous diseases, elephantiasis, tuberculosis, chronic bronchitis, asthma, anemia, amenorrhea, dysmenorrhea, menorrhagia, eczema, leprosy, anorexia, fracture of bones, and osteoporosis [Anisimov and Shakirzyanova, 1982; Nigam et al., 1984; Acharya et al., 1988; Bhattacharya, 1995]. Mumie is useful as an aphrodisiac, rejuvenator, alternative tonic, internal antiseptic, diuretic, lithontriptic [Rasulov, 1964; Kozlovskaya, 1968; Acharya et al., 1988]. Mumie can be applied as a remedy for the above-mentioned and some other disorders both as an independent preparation and as a component of herbomineral formulations (drugs and manufacturers, including location of manufacturers, are listed in Table 1).

Different companies manufacturing crude extract of mumie give their recommendations regarding the application of this preparation for humans. Best Nutrition Products (United States) recommended the following regimen for adults: 0.2 g of mumie extract, per os, two to three times a day for 25–30 days during intense training or stress; repeat course after 1–2 weeks. Russian doctors recommend administration of mumie for treating children depending on their age: from 3 months to 1 year: 0.01–0.02 g/day, from 1 to 5 years: 0.03–0.04 g/d, from 5 to 9 years: 0.05 g/d, from 9 to 14 years: 0.1 g/d.

Successful application of mumie in folk medicine as a remedy for many diseases focused the attention of researchers on studying the therapeutic properties and chemical composition of this multi-component natural substance.

Influence of Mumie on Enzyme Activity, Ion Transport, and Free Radical Processes

Mumie (0.2–0.8 mg/ml) activates mitochondrial respiration but suppresses activity of succinate-oxidase and NADH-oxidase in mitochondrion [Almatov and Akhmerov, 1977]. It is assumed that the stimulating action of Mumie is caused by activation of Ca^{2+} transport. Mumie induces a dose-related increase in superoxide dismutase, catalase, and glutathione peroxidase activities in frontal cortex and striatum of rats [Ghosal et al., 1993; Bhattacharya et al., 1995; Ghosal and Bhattacharya, 1996].

Processed extract of mumie efficiently traps hydroxyl radicals, $NO\cdot$ and $SO\cdot$ radicals and also has the ability to regenerate ascorbic acid [Ghosal, 1995]. Mumie is an inhibitor of lipid peroxidation induced by cumene hydroperoxide and ADP/Fe^{2+} complex in a dose-dependent manner. It decreases the rate of oxidation of reduced glutathione and inhibits ongoing lipid peroxidation, induced by these agents, immediately after its addition to the incubation system [Tripathi et al., 1996]. Antiradical properties of mumie extract can be attributed to the presence of dibenzo-α-pyrones and fulvic acid [Wang et al., 1996]. It is

assumed that the therapeutic properties of some multicomponent preparations, containing mumie in their composition, are caused by antiradical properties of this humus matter [Mitra et al., 1996a; Bhattacharya et al., 1997].

Antibacterial activity

Mumie possesses the antimicrobial activity with respect to different strains of the widespread pyogenic microbes (staphylococci, streptococci, coliform bacteria, enterococci, Proteus) [Shakirov, 1967, 1969] and is applied for treatment of suppurative wounds [Muratova and Shakirov, 1968]. The bactericidal activity of mumie extract may be related to some of its components, such as benzoic and fulvic acids [Van Rensburg et al., 2000]. The clinical studies carried out in Kazakhstan Tuberculosis Institute (Almaty) showed that the application of mumie extract (patented name "Olepet") for complex treatment of 300 patients with pulmonary tuberculosis shortened the treatment period by three to four times as compared with traditional chemotherapy.

Mumie as Anabolic Agent

To reach the anabolic effect of mumie extract, the short-term cycles were used (0.3–0.6 g/d, for 10–12

TABLE 1. Pharmaceutical Companies Producing Medical Drugs From Mumie, Peat, and Sapropeles

Medical Drug	Company	Company Location (City/State/Country)
Abana (HeartCare)	Hymalaya Drug Company	Banglore, India
Adrenotone	Rockwell Nutrition Company	Miami, FL
	Gaines Nutrition	Redlands, CA
Andro-Surge	Mineral Connection	Taylor, TX
Cystone (UriCare)	Ayurvedic Concepts	Segamat, India
	Hymalaya Drug Company	Banglore, India
	Stichting EISRA	Den Haag, The Netherlands
Diabecon D-400	Hymalaya Drug Company	Banglore, India
EveCare	Hymalaya Drug Company	Banglore, India
GeriCare	Hymalaya Drug Company	Banglore, India
Geriforte	Hymalaya Drug Company	Banglore, India
Kidney Formula	Banyan Botanicals	Albuquerque, NM
La-Tone Gold	LA-Medica, Pvt. Ltd.	Calcutta, India
Lukol	Indousplaza	New York, NY
	Hymalaya Drug Company	Banglore, India
Mumie	Ehinops	Sevastopol, Ukraine
	Evalar	Biysk, Russia
Mumie-Vitamustim	Avicenna	Moscow, Russia
Nefrotec	Hymalaya Drug Company	Banglore, India
Pilex (VeinCare)	Hymalaya Drug Company	Banglore, India
Rumalaya (JointCare)	Hymalaya Drug Company	Banglore, India
Shilagen	Sandusky's Health Alternatives	Sylvan Lake, Alberta, Canada
	Crucible Catalog	Sacramento, CA
Shilajit	Dabur India, Ltd.	New Delhi, India
	FabriChem	Fairfield, CT
	Aarogya Herbals (P), Ltd.	New Delhi, India
	SDR Shilajit	Amritsar, Punjab, India
Siotone	Albert David, Ltd.	Calcutta, India
	Resources International	Lexington, KY
Solanova Libidoplex	Wellness Tools	Colorado Springs, CO
	Solanova	Novato, CA
	Metafoods	Cottonwood, AZ
	Eckhart Corp.	Novato, CA
Somatomed (VesPro GHS)	VesPro Life Sciences	Overland Park, KS
StressCare	Hymalaya Drug Company	Banglore, India
Tentexforte	Hymalaya Drug Company	Banglore, India
Eplir	Biolit	Tomsk, Russia
FiBS	Biostimulator	Odessa, Ukraine
	Farmak	Kiev, Ukraine
Humisol	Tallinna Farmaatsiatehas	Tallinn, Estonia
Peloidodistillate	Biostimulator	Odessa, Ukraine
Tolpa Peat Preparation (TPP)	Torf Corp.	Wroclaw, Poland

days) in sportsmen. These cycles are often repeated three to four times after a 15–20-day break. The effect includes activation of anabolic processes on cell and molecular levels in different organs and tissues [Gupta et al., 1966]. Experimental investigations showed that mumie extract (0.5 g/kg, per os, daily, for 10 days) accelerated processes of protein and nucleic acid synthesis, stimulated the energy-providing reactions in liver, and promoted transportation of minerals, especially calcium, phosphorus, and magnesium, into muscle and bone tissues [Shvetskii and Vorobeva, 1978]. Studies of anabolic properties made it possible to use mumie extract in elite Russian military and sports establishments for nearly 4 decades for increasing strength and muscle mass as well as for its recuperative powers.

Mumie extract is a constituent part of several multi-component anabolic preparations, such as VesPro GHS (Somatomed), Andro-Surge and Geriforte [Dubey et al., 1980].

Mumie as Adaptogen

Mumie extract is an adaptogenic agent that protects the human physiological system against diverse stressors and improve restoration (recovery) after exercises. However, it did not significantly change floating time on the swimming test in mice [Bose and Gupta, 1999]. Mumie extract is included in composition of several multicomponent drugs with adaptogenic activity, such as Adrenotone, Siotone, StressCare, and Geriforte [Dubey et al., 1984a; Bhattacharya et al., 2000].

Effect of Mumie on Endocrine System

Mumie contains steroid-like compounds; among them are sterols and dibenzo-α-pyrones. Plant sterols could be incorporated into mumie in humin bound form [Lichtfouse, 1999]. Mumie extract may act as an antidiabetic agent and can enhance the level of growth hormone in diabetic patients. It is a component of complex drugs VesPro GHS (Somatomed) and Andro-Surge that stimulate the human organism to produce more of its own growth hormone and testosterone.

Application of Mumie for Stimulation of Regeneration Processes

Mumie is highly effective in the treatment of thermal burns [Foigelman, 1972] and stimulation of hepatic regeneration after CCl_4 administration [Vaishwanar et al., 1976]. After burn injury, the application of mumie extract causes a decrease in pain, disappearance of inflammation, shortening of the periods of scab rejection and wound purification from the necrotic tissues, appearance of granulations, and early epithelization [Anisimov and Shakirzyanova, 1982]. The use of mumie (0.6 g/d, per os, for two 10-day cycles with 1-week break) for treating for postoperative cavities in 50 patients with chronic suppurative otitis contributed to the more rapid healing of trepanation cavity of the tympanum [Psakhis and Aizenberg, 1976]. It is possible that the positive role of mumie extract is caused by its stimulating action on bone regeneration. Ukrainian doctors used mumie for rehabilitation of patients after operation for vertebral–cerebrospinal injury [Perederko et al., 1998]. A significant positive action of mumie (irrigation by 0.5% water solution of mumie, daily, for 1 week) was noticed during the rehabilitative treatment after tonsillectomy [Gordievskii and Barulina, 1974].

Mumie extract (0.1 g/kg, daily) caused acceleration by 20–25% of primary callus formation on the focus of bone fracture of long bone in rabbits [Ismailova, 1965; Shakirov, 1965a; Kelginbaev et al., 1973]. Mumie in the same doses led to an increase of [^{32}P] uptake by 3–3.5 times on the focus of fracture [Shakirov, 1965b]. According to data of Tkachenko et al. [1979], the effect of mumie extract on bone regeneration in guinea pigs after fracture can be different depending on the dose of the preparation and time elapsed after operation. The maximum intensification of regeneration was observed when mumie was applied daily on the early periods after operation (1–7 days) at the dose of 0.3 g/kg. Under these conditions, mumie caused twofold intensification of osteoid formation and bone mineralization. Administration of mumie in these doses 2–3 weeks after operation was accompanied with reducing of osteoid mineralization by seven times [Tkachenko et al., 1979]. It was reported that mumie extract acted favorably on bone regeneration after fractures in children [Kelginbaev et al., 1973] and in patients subjected to surgery for osteoarticular tuberculosis [Suleimanov, 1972].

Antiinflammation Properties

Mumie extract is highly effective during treatment for paradontosis in humans [Habilov, 1971] and has significant antiinflammatory effect on osteoarthrosis, rheumatoid arthritis, ankylosing spondylitis, and cervical spondylosis [Soliev, 1983]. In folk medicine and clinics, mumie is used to treat patients for peptic ulcer (0.3 g/d, for 20–25 days). It is suggested that antiulcerogenic activity of mumie extract is determined by its antihistamine and antiserotonin effects. Antiulcerogenic activity of mumie extract was confirmed by experiments [Kozlovskaya, 1971]. Crude extract of mumie at the dose of 0.05 g/kg suppressed carrageenan-induced acute pedal edema (to 77%), granuloma pouch and adjuvant-induced arthritis in rats [Goel

et al., 1990]. It is also possible that antiinflammatory and antiulcerogenic properties of mumie can be explained by the presence of benzoic acid (up to 7–8%), fulvic acids, 4′-methoxy-6-carbomethoxybiphenyl, and tirucallane-type triterpenoids in its composition. These compounds are known to possess strong antiinflammatory properties [Ghosal et al., 1988, 1991b; Alam and Gomes, 1998; Rajic et al., 2001]. Due to bacteriostatic and antiinflammatory action, mumie extract facilitates the process of wound cleaning from necrotic tissues, granulation, and epithelization, and decreases the period of wound healing [Tazhimametov et al., 1987].

Immunomodulation and Antiallergic Properties

Application of mumie causes proliferation of lymphocytes of cortical thymus layer, and their intensive migration into thymus-dependent zones of lymph nodes and spleen [Agzamov et al., 1988]. Mumie extract activates macrophage cell migration in epithelioid granulomas in struck pulmonary tissue with experimental tuberculosis [Agzamov et al., 1988]. The specific epitheliocellular granulomas were transformed to macrophageal ones after mumie application. It was shown that the remedy promoted renewal of capillaries in inflammation focus and periphery, increased resorption of necrotic lesions and infiltrates, and improved transport of antibacterial drugs to the inflammation foci [Agzamov et al., 1988]. It is important that the preparation activates phagocytosis and releases cytokines in mouse peritoneal macrophages [Ghosal, 1990; Bhaumik et al., 1993]. The administration of mumie extract in the dose of 0.5 g/kg from the 1st to the 20th day after γ-irradiation (180–220 r/min, dose 600 r) stimulates lymphopoietic erythropoiesis in acute radiation disease. This is manifested by a more rapid restoration of the number of lymphocytes in peripheral blood, bone marrow, and spleen [Rogozkin and Tukhtaev, 1968]. Interestingly, for stimulation of immunity, in the Leningrad Zoo (St. Petersburg, Russia) chinchilla puppies were bottle-nursed with addition of mumie solution [Volkova, 2000].

Because mumie contains biphenyl and benzocoumarin compounds, which have significant antiallergic activity, mast cells are stabilized by mumie extract and have significantly less degranulation [Ghosal et al., 1988; Bhattacharya et al., 1989]. Positive results were obtained during the treatment for eczema and psoriasis (0.2 g/d, per os, two 10-day cycles with 5-day break) [Anisimov and Shakirzyanova, 1982].

Influence of mumie on central and peripheral nervous system

Mumie was used in Indian medicine to attenuate cerebral functional deficits, including amnesia, in geriatric patients. It was shown that this remedy promoted learning and memory [Bhattacharya and Ghosal, 1992; Jaiswal and Bhattacharya, 1992; Ghosal et al., 1993]. Administration of mumie extract (in doses of 0.04 g/kg for 7 days) decreased acetylcholinesterase activity restricted to the basal forebrain nuclei including medial septum and vertical limb of diagonal band in rat brain [Schliebs et al., 1997]. Mumie extract was considered as a prospective inhibitor of analgesic tolerance to morphine [Tiwari et al., 2001]. Treatment with mumie affected neither γ-aminobutyric acid (GABA) and benzodiazepine receptor binding nor NMDA and AMPA glutamate receptor subtypes in any of the cortical or subcortical regions, but increased muscarinic acetylcholine M_2 receptor binding [Schliebs et al., 1997]. Transina, an Ayurvedic herbal formulation comprising *Withania somnifera, Tinospora cordifolia, Eclipta alba, Ocimum sanctum, Picrorrhiza kurroa*, and mumie, exerts significant nootropic effect after subchronic treatment of rats (0.2 or 0.5 g/kg, per os, daily, for 21 days) that may be due to reversal of perturbed cholinergic function [Bhattacharya and Kumar, 1997]. Nevertheless, in the literature several cases were described when mumie application in treating neurologic diseases (multiple sclerosis) led to deterioration in patient state [Magidzon and Khmelevskii, 1982].

Mumie extract was recommended as an effective drug in treatment for radiculitis, plexitises, and neuralgias of different etiology [Kozlovskaya, 1968; Mamadjanov, 1975; Akhmedov and Aminov, 1979; Anisimov and Shakirzyanova, 1982]. In treating trigeminal nerve neuralgia, a combined procedure was used with the application of electrophoresis with 2% lidocaine and 4% mumie solution (in water) (10–12 times). Most of the results were remarkably positive, which was especially noticeable in the case of the neuritic stage of neuralgia with the central genesis and, in case of neuralgia, with predominantly peripheral genesis [Grechko et al., 1985].

Other Therapeutic Properties of Mumie

The mumie extract exhibited significant inhibition in the proliferation of the Ehrlich ascites tumor cells [Ghosal, 1990]. The preparation reduces the increased level of cholesterol in the blood and increases the removal of cholesterol with the bile. Mumie application with acute thrombophlebitis improves the general state of patients, decreases edema and pain, and leads to improvement in vessel pulsation and normalization of blood coagulability [Anisimov and Shakirzyanova, 1982]. Application of mumie under the conditions of intoxicating the animals by lead salts contributed to removal of this poison from the liver. The intravenous application of Caucasian mumie (2.5% solution in

water, 50 mg/ml/d, for 10 days) abolished the hematotoxic effect of thiotepa, a cytostatic agent that has been used in the treatment of malignant lymphomas and solid tumors [Kozlovskaya, 1972].

Mumie Toxicity

Mumie extract does not cause any mortality in mice up to the dose of 1 g/kg (intraperitoneal injection) [Acharya et al., 1988]. For toxicological study, the experimental animals received the preparation daily in the form of 1–10% aqueous solution (orally) for 1 month. The daily doses of mumie extract for rabbits and mice were 0.05, 0.1, 0.15, 0.2, 0.3, 0.4, and 0.5 g/kg. On its application both once (0.5 g/kg) and on a multitime basis (total dose was from 1.5 to 15 g/kg) the investigators did not observe any morphological or histological changes in the internal organs of animals in comparison with the control group [Kelginbaev et al., 1973].

In the Ukrainian Gerontology Institute (Kiev), the study of toxicological properties of mumie picked from alpine regions of Central Asia was carried out. It was found that application of the remedy at the doses of 0.2 and 1 g/kg for 3 months did not lead to negative influence on the function of heart, liver, kidneys, blood cells, or nervous and endocrine systems. The study of specific teratogenic action showed that treatment of pregnant rats with mumie did not render embryotoxic or teratogenic actions. The postnatal development of young rats, whose parents received the preparation, was also normal.

Most of the investigators noted absence of side effects with mumie application at daily dose of 0.1–0.3 g inwardly. Some patients with bone fractures felt burning in the region of fracture. Patients with chronic colitis felt heat, burning, weakness, and sweating during 40–60 min after application of mumie extract. At higher doses (0.9-1.5 g/d) it can lead to increase in body temperature to 37.5°C, sweating, and headache. The duration of this reaction was from 20 min to 2–3 h [Anisimov and Shakirzyanova, 1982].

The use of standardized mumie extract provides the best opportunity of getting a positive result. Shilagen contains mumie that is standardized to contain at least 20% of fulvic acids is the new leader in high potency natural fulvic acid supplements. Raw mumie contains 0.01% wt/wt of dibenzo-α-pyrones. Their content enhances to 1% (wt/wt) in processed mumie extract. Standardization of mumie extract to contain 20% of fulvic acids and 1% of dibenzo-α-pyrones would ensure consistent nootropic activity, high immunomodulation, and very effective antioxidant activity [Ghosal and Bhattacharya, 1996]. The processing needs to remove free radicals, toxins, mycotoxins, and inactive ingredients.

Medical Drugs of Mumie

The pharmaceutical companies in India (Dabur, Aarogya Herbals (P) Ltd.), the United States (Fabri-Chem, Triple Crown), Ukraine, Kazakhstan, and Russia produce purified mumie extract without other biologically active additions (drugs: Shilajit, Mumie-Vitas, Olepet, Mumie), or mumie extract included in compositions of complex herbal and mineral formulas. Some of these preparations resulted from the development of Ayurvedic conceptions, the others were devised by contemporary research and patented. For example, Rowland [1999] suggested the mixture of vitamins, minerals, and mumie. Mumie is used in composition formulas of Shilagen, Abana (HeartCare), Cystone (UriCare), Diabecon 400, EveCare (MenstriCare), Geriforte (GeriCare/StressCare), Lukol, Pilex (VeinCare), Rumalava (JointCare), Tentex forte (VigorCare-Men), Nefrotec, Adrenotone, Siotone, La-Tone Gold, Andro-Surge, Solanova Libidoplex, and Renone cream [Jadhav and Bahga, 1971; Mardicar, 1975; Bhatta, 1982]. The content of mumie in some medical formulations is shown in Table 2.

Shilagen includes proven healing substances such as ashwagandha, ginkgo biloba, bacopin, and trace minerals to aid in the absorption and synergy of the primary mumie ingredients. The producers of Shilagen use a patented oxygen/nitrogen displacement extraction process that ensures the proper pH and increases the effectiveness of active ingredients of mumie by approximately 800%. They also use a standardized extract, so equal high levels of active ingredients are in each bottle. Shilagen has been recommend to treatment the same disorders for which mumie extract is applicable.

Mumie is incorporated in the herbal formula of *Adrenotone* that includes Chinese herbs used for centuries. Adrenotone has been recommend as a remedy to naturally support the adrenal function, high energy levels, and overall wellness during times of stress or immune weakness [Ziauddin et al., 1996]. Adrenotone is produced and distributed by Rockwell Nutrition Company and Gaines Nutrition.

Siotone is an herbal formulation in Ayurvedic medicine. It consists of components all of which, including mumie, are known to promote physical and mental health, and improve immunity. A study was undertaken to investigate the adaptogenic activity of Siotone against chronic unpredictable, but mild, foot-shock stress-induced disturbances in behavior in rats. Siotone (200 mg/kg, in mice) revealed significant decrease of chronic fatigue induced by Porsolt's forced

TABLE 2. Amount of Mumie in the Various Medical Formulations

Medical formulation	Weight of mumie (mg/capsule)	Percent of mumie (weight %; mumie per total active ingredients in the capsule)	References
Adrenotone	25	3.8	Ziauddin et al., 1996
Andro-Surge	50	22.6	The Mineral Connection Co.
Cystone	13	5.8	Singh et al., 1985
D-400	30	7	Sundaram et al., 1996
La-Tone Gold	30	4.6	LA-Medica Pvt Ltd.
Lukol	9	3	Gupta and Bhanot, 1973
Pilex	16	6	Misger et al., 1977
Rumalaya	16	4.2	Singh et al., 1984
Siotone	250	16.1	Bhattacharya et al., 2000
Tentex Forte	32	9.7	Bhatta, 1982

swimming test [Kaur and Kulkarni, 2000]. Siotone in granules (100 and 200 mg/kg) proved to be a good protector against convulsions induced by pentylenetetrazol, maximal electroshock, and strychnine. In hypoxic stress-induced convulsions, only 200 mg/kg were effective. The anticonvulsant action of Siotone granules was blocked by flumazenil (4 mg/kg), suggesting the involvement of a GABA-ergic mechanism [Kulkarni and Joseph, 1998a]. An extensive study of Siotone granules demonstrated its central nervous system depressant effect as well as its beneficial effect in anxiety and cognition in animals [Kulkarni and Joseph, 1998b]. Chronic stress-induced increase of tribulin activity in rat brain was also reversed by these doses of Siotone [Bhattacharya et al., 2000]. The drug is produced by Resources International.

La-Tone Gold is useful in treatment of sexual impotence. La-Tone Gold provides a rapid arousal by exerting generally stimulating and enhancing influence on the function related to the reproductive system that promotes enhanced genital blood circulation and engorgement, euphoria, and a satisfying tumescence besides improving stamina in males. La-Tone Gold is produced by LA-Medica Pvt Ltd..

Andro-Surge is an herbal formulation designed for optimal regulation of anabolic hormones and testosterone levels. This formula is recommended for male athletes, being especially effective for those over 38 years of age, or for adults with low levels of dehydroepiandrosterone. Andro-Surge is produced by Mineral Connection.

Solanova Libidoplex is a synergistic blend of specific herbal extracts and vitamins. It is a very powerful virility-enhancing formula designed to heighten energy and stamina. It can also be used as an overall body tonic. Benefits both men and women and is especially safe for use by women. Solanova Libidoplex is produced and distributed by Eckhart Corp., Solanova, and Metafoods.

Evecare (U-3107) is herb-mineral uterine tonic formulated by Himalaya Drug Company. The herbs used in this tonic are effective in various menstrual disorders. These components acting alone and in combination are responsible for the efficacy of the drug in dysmenorrhea, menorrhagia, and other uterine disorders [Mitra et al., 1998].

Mumie is one of the components of *StressCare* and *GeriCare*. StressCare is useful in stress-related conditions such as premature aging, fatigue, insomnia, or emotional imbalance. GeriCare is the ultimate general fitness product that promotes health and helps everyone to age gracefully without any adverse effects.

Geriforte is a completely natural product that regulates and balances all the body organs and systems for comprehensive health care maintenance. Geriforte is used as a restorative tonic to solve the problems of old age in India. Geriforte administration stimulates the antioxidant defense system [Pathania et al., 1998]. Antistress and anabolic properties of this drug were denoted in many reports [Singh et al., 1978; Dubey et al., 1980, 1984a]. Geriforte (feeding for 4 weeks) significantly increased catalase, superoxide dismutase, and glutathione peroxidase activities in liver of mice. In rats, in addition to these enzymes, the levels of reduced glutathione were also significantly enhanced [Pathania et al., 1998]. The contents of superoxide dismutase and catalase in brain of Geriforte-administered animals were increased by 24% and 30%, respectively [Singh et al., 1994].

Mumie is used for urinary disorders or stones in combination with *Kidney Formula.*

Renone cream is an external application ointment formulated for greater relief from muscular pains, joint pains, swelling, and inflammation. It is an exclusive

combination of many reputed and time-tested pain-relieving herbs and ingredients.

Lukol is an indigenous preparation, which is administered orally in the form of tablets for the treatment of leukorrhea. It is claimed to be completely free from toxic effects. The therapeutic value of Lukol in the oral therapy for nonspecific leukorrhea, menorrhagia, and other associated symptoms was established by several clinical trials in India [Bhagwat, 1962; Dabak et al., 1984].

Diabecon D-400 is a herbomineral formulation, main components of which among others are mumie, *Gymnema sylvestre, Pterocarpus mascupium, Casearia esculanta, Eugenia jambolana, Ocimum sanctum*, and *Momordica charantia* [Mitra et al., 1995a, 1995b, 1996a, 1996b]. Diabecon significantly potentiates the hypoglycemic action of insulin in alloxan-induced diabetic rats [Anturlikar et al., 1995]. Diabecon therapy caused a significant increase in islet number and beta cell count and appeared to bring about blood sugar homeostasis by increasing insulin secretion and regeneration of endocrine pancreas [Mitra et al., 1996c]. Clinical application of Diabecon showed that it can be used alone or as adjuvant in non-insulin-dependent diabetes mellitus patients, because it significantly reversed the changes in early diabetic retinopathy [Mitra et al., 1995b; Sundaram et al., 1996]. Experimental trials testify that Diabecon has a nephroprotective action against alloxan-induced renal damage in rabbits [Dubey et al., 1994]. Streptozotocin-induced histopathology changes in pancreas and liver of rats, as well as a decrease in pancreatic islet cell superoxide dismutase, were partially reversed by Diabecon. It was suggested that Diabecon helps in improving the glycogen stores in the liver and prevents the streptozotocin-induced damage through free radical scavenging activity of mumie extract [Mitra et al., 1996c].

Cystone, a patented herbal drug formulation, is claimed to maintain crystalloid–colloid balance and to dissolve the stone matrix, thereby disintegrating renal, bladder, and gall stones [Singh et al., 1985]. Cystone has been clinically used extensively for complex treating for many urinary tract complications such as urolithiasis [Rai, 1960; Khan, 1983], burning micturition [Garg and Singh, 1985], neuroureterolithiasis [Misger, 1982], urinary tract complications in pregnancy [Sengupta, 1987], urinary tract infections [Srivastava et al., 1991], and other urinary tract disorders [Chatterjee, 1982; Sharma et al., 1983]. Cystone has been shown to provide partial but significant protection against renal toxicity induced by the antitumor agent cisplatin in rats and mice [Rao and Rao, 1998; Rao et al., 1999]. The protection may be mediated through its ability to inhibit lipid peroxidation. In fact, Cystone inhibited the lipid peroxidation in renal cortical slices induced by cisplatin [Rao and Rao, 1998]. Cystone is manufactured by Ayurvedic Concepts (Bangalore, India) and Himalaya Drug Company.

Abana is an herbomineral medicinal preparation with the property of downregulation of β-adrenergic receptors. The therapy with Abana proved to be highly effective in hypertensive patients [Dadkar et al., 1990]. Administration of Abana for 3 days increased the basal amplitude and reduced the responses of atria to isoprenaline and norepinephrine in rabbits [Pasnani et al., 1988]. Abana pretreatment potentiated the inotropic responses of histamine and $CaCl_2$. These effects may be due to a specific depressant effect of Abana on the adrenergic receptors and to direct sensitization of the atrium manifested by the increased response to $CaCl_2$ [Pasnani et al., 1988]. Abana seems to reduce preload and afterload and improve diastolic and pump functions of heart that may be responsible for beneficial effect of Abana in patients with ischemic heart disease [Antani et al., 1990]. Histological pictures showed pronounced reduction in the atherosclerotic involvement of the coronary artery in rabbits with an atherogenic diet following treatment with Abana [Tiwari et al., 1993]. Abana protects mice against radiation-induced micronucleus formation and radiation-induced decline in cell proliferation [Jagetia and Aruna, 1997].

Pilex tablets are used for relief of hepatic congestion. The drug reduces venous engorgement and turgidity, tones up the venous walls, reduces portal pressure, prevents bleeding and inflammation, and is a mild laxative [Rangnekar and Arora, 1975; Misger et al., 1977].

Rumalaya is an indigenous formulation whose components, including mumie, have antiinflammatory and antiarthritic properties [Rao and Gupta, 1977]. Rumalaya was tested and found to be useful in various orthopedic problems such as osteoarthritis of the knee joints, rheumatoid arthritis, ankylosing spondylitis, and cervical spondylosis. Ramalaya provided significant clinical improvement in the case of low backache, e.g., spondylolisthesis, spina bifida, and prolapsed intervertebral disc [Singh et al., 1984]. Dubey and co-workers noticed a significant decrease in duration and intensity of pain, more pronounced in fibrositis cases than in sacroiliitis and spondylitis ones [Dubey et al., 1984b]. This drug did not cause any side effects even after continuous oral administration [Dubey et al., 1984b]. Rumalaya is manufactured by Himalaya Drug Company.

VesPro GHS (Somatomed) is a patented drug that stimulates the organism to produce more of its own human growth hormone as well as other important

antiaging hormones. Each tablet contains a nonhormonal herbal base of mumie, licorice, schizandra, and *Tribulus terrestris*. VesPro GHS was found to be a safe and efficacious drug capable of improving many of the clinical signs and symptoms associated with the chronic fatigue syndrome.

CONSTITUENTS OF MUMIE, SAPROPEL, AND PEAT

The main substances that are formed in the process of plant humification are fulvic and humic acids. They comprise a chemical and physical heterogeneous group of high-molecular-weight hydroxylated polyphenolic compounds with colloidal, polydispersed, and polyelectrolyte characteristics and a mixed aliphatic and aromatic nature [Senesi and Loffredo, 1999]. These acids are found abundantly in peat, sapropel, mumie, and other humus matters, being of medicinal importance.

At present, three theories of plant humification exist. According to the lignin theory, lignin is incompletely utilized by microorganisms with the generation of *o*-hydroxyphenols and oxidation of aliphatic side chains to form COOH groups. The modified material is subjected to further unknown changes to yield first humic acids and then fulvic acids [Waksman, 1938]. In an aerobic microenvironment, lignin may be broken down into low-molecular-weight products. According to the polyphenol theory, phenolic aldehydes and acids released from lignin or nonlignin sources (e.g., cellulose) during microbiological attack undergo enzymatic conversion to quinones, the latter polymerize in the presence or absence of amino compounds to form dark-colored polymers [Kononova, 1966]. According to the sugar–amine condensation concept, reduced sugars and amino acids formed as byproducts of microbial metabolism undergo nonenzymatic polymerization to form brown nitrogenous polymers [Stevenson, 1994]. An attractive feature of this theory is that the reactants (sugars, amino acids, etc.) are produced in abundance through the activities of microorganisms. The drastic and frequent climatic changes in mountain regions (freezing and thawing, wetting and drying), together with the intermixing of reactants with mineral materials having catalytic properties, may facilitate condensation and mumie formation (Fig. 1). The composition of fulvic and humic acids in natural organic-mineral matter vary with geographic location. In particular, peat and mumie are exposed to a higher oxygen influence than sapropel, which is permanently submerged. This leads to intensification of oxidation processes and to changes in chemical and biological characteristics of humic and fulvic acids [Orlov, 1995; Esteves and Duarte, 2000].

It was hypothesized that the nonpolar groups in the molecules of humus substances formed micellar or double-layer structures that trap the nonpolar organic in a microscopic hydrophobic environment similar to the behavior of surface-active micelles [Wershaw, 1986]. The structure of the humin complex explains the stabilization of soil organic matter by binding functional biomarkers and encapsulation of small polar molecules [Lichtfouse, 1999]. In fact, the mumie extracts were shown to possess a lattice-like structure perforated by voids of varying dimensions (10–50 μm) [Ghosal et al., 1991a]. These are filled with organic molecules or metal complexes that may be responsible for therapeutic effects. Degrading the humus samples of mumie and analysis of the products spectroscopically shows that they are structurally similar to ordinary soil.

Although it is now widely accepted that mumie, peat, and sapropel extracts can be valuable in conventional medicine, the other way forward is to formulate drugs using the active constituents, rather than to use crude natural extracts. This makes it feasible to do research directed to isolation of active ingredients from natural organic–mineral matter and to study the opportunity of using them individually or in combinations with each other. In particular, a preliminary screening showed that a lipid concentrate extracted from a silt-sulphide sapropel exhibits the highest antioxidative activity [Pisareva et al., 1997]. The lipid concentrate from sapropel was shown to have an antimetastatic effect and it reduced hematotoxicity of cyclophosphane [Burkova et al., 1995].

Characteristics and Pharmacological Properties of Fulvic and Humic Acids

The therapeutic properties of fulvic and humic acid are similar to the properties of crude extracts from peat, sapropel, and mumie. Fulvic and humic acids are panaceas of oriental medicine where they continue to be used extensively for treatment for cold stress, diabetes, skin diseases, rheumatic pain, kidney stones, heart ailments, leprosy, and immune system diseases. Many reports on the beneficial use of fulvic acids for medicine have been published. These include reports documented in a Chinese pharmacological compendium dating from the 15th century. The reports deal with the drug "Wujinsan" containing humic and fulvic acids, implying that these substances are efficient antiinflammatory and blood-coagulating agents. Fulvic acids possess antiallergic action by the mechanism of mast cell protection. Experimental study testified that oxyfulvic acids are effective in the topical treatment of traumatic and chemical dermatitis in cats, dogs, and mice [Dekker and Medlen, 1999; Van Rensburg et al.,

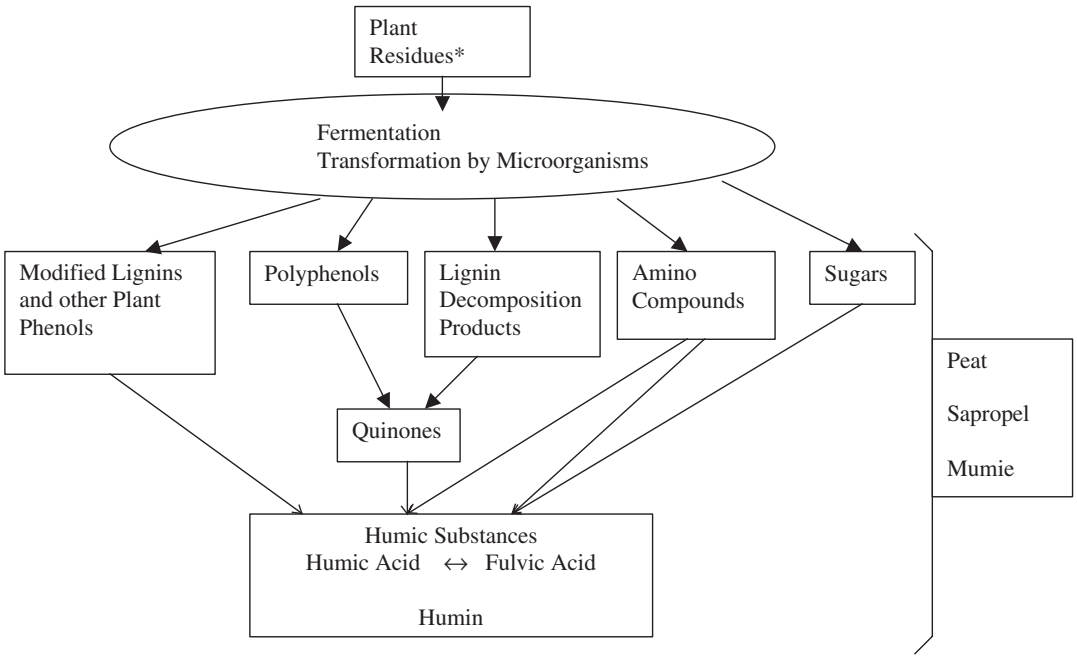

Fig. 1. Schematic diagram of humic substance formation for peat, sapropel, and mumie (*for the formation of sapropel humus matter, the phytozooplankton litter also plays an important role, together with plant residues).

2001]. Neither sensitizing nor irritating properties were detected in the concentrations of up to 10% in humic acid solution [Wiegleb et al., 1993]. Humic and fulvic acids were used as externally applicable drugs in the clinical treatment for hematoma, phlebitis, desmorrhexis, myogelosis, arthrosis, polyarthritis, osteoarthritis, and osteochondrosis [Laub, 1999]. With respect to internal use, fulvic and humic acids have been shown to be particular useful in therapy for gastritis, diarrhea, stomach ulcers (antiulcerogenic and antistress activity), dysentery, colitis, and diabetes mellitus [Yudina et al., 1996, 1998b; Laub, 1999]. Experimental and clinical results demonstrate that fulvic and humic acids stimulate osteoclastic resorption of transplanted bones as well as hydroxyapatite used for bone substituent [Schlickewei et al., 1993].

The antimicrobial activity of fulvic acid was described by van Rensburg et al. [2000]. In that study, all eight microbial pathogens were tested (*Staphylococcus aureus, Streptococcus faecalis, Pseudomonas aeruginosa, Escherichia coli, β-haemolytic streptococcus, Klebsiella pneumoniae, Proteus mirabilis*, and *Candida albicans*) and found to be sensitive to oxyfulvic acid at concentrations $\leq 1.5\%$. Ammonium humate isolated from peat water is a higher molecular polyphenolic compound with a strong antiviral activity against herpes simplex virus type 1 and type 2 (at humate concentrations 0.5–20 μg/ml) and influenza virus type A and B [Thiel et al., 1977; Schiller et al., 1979; Thiel et al., 1981; Hils et al., 1986]. Fulvic and humic acids also increase number and functional activity of macrophages, neutrophils, and killer T-cells [Riede et al., 1991; Laub, 1999].

Humic acids were found to inhibit the mutagenicity of benzo[a]pyrene, 2-aminoanthracene, 2-nitrofluorene, and 1-nitropyrene in the *S. typhimurium* test. Desmutagenic effect was caused by adsorption of mutagenes by humic acids [Sato et al., 1987]. Humic acids shortened prothrombin time, activated thromboplastin period [Lu et al., 1990], and inhibited plasma protein C activity [Yang et al., 1994]. Humic acid is involved in tissue factor induction and plasminogen activator inhibitor synthesis in human umbilical vein endothelial cells [Yang et al., 1996]. Sodium humate was found to raise the activity of plasminogen activator [Klocking et al., 1984]. In the experiments on the chronic effects of humic acid in vivo, it was found that humic acid caused peroxisome proliferation in mouse liver, increased the activities of hepatic acyl-CoA oxidase, carnitine palmitoyltransferase, and carnitine acetyltransferase in rats [Lu et al., 1994; Lee et al., 1999].

About 50 years ago, professor Khristeva first discovered the high efficiency of humates as fertilizers and anabolic substances, which was supported by the following investigations. Sodium humate introduced into chickens increased body mass by 5–7% on average and poultry safety by 3–5% [Khristeva, 1951; Stepchenko et al., 1991; Zhorina and Stepchenko, 1991].

Fulvic acids are powerful antioxidants and possess superoxide and hydroxyl radical scavenging properties [Wang et al., 1996]. They are excellent natural chelators and cation exchangers [Schnitzer and Khan, 1972]. Fulvic acids may also have a physiological role, acting as carrier molecules or chelating agents for the more bioactive smaller compounds [Ghosal et al., 1991a]. Fulvic acids can be accumulated in tissues as semiquinone radicals [Peng et al., 1992, 1999] and behave as electron donors or acceptors, depending on the redox state of the system [Senesi et al., 1977; Sposito et al., 1982; Pardoe et al., 1990]. Besides, fulvic and humic acids modified the toxic behavior of various organic xenobiotics, impacting their transport into the cell interior. A single administration of sodium humate 5–10 min after irradiation with the dose of 193.5 mCi/kg leads to 43.3% survival of animals after 60 days; with the dose of 232.2 mCi/kg, there is a trend toward an increase in the lifespan of exposed rats [Pukhova et al., 1987]. Either an increase or reduction in toxicity was observed in the presence of humic substances [Herzig et al., 1994; Perminova, 1999]. Humic acid at concentrations ranging from 10 to 100 μg/ml caused lipid peroxidation in a dose-dependent manner. Such changes were accompanied by a depletion of glutathione and a reduction in activities of the antioxidant enzymes including catalase, superoxide dismutase, and glucose-6-phosphate dehydrogenase [Cheng et al., 1999]. Thus, the final biological effect of humus substances can be determined by the quantity of fulvic and humic acids, and redox state of the test biological system.

Fulvic acids have lower molecular weights (0.5–2 kDa) and a smaller number of total and aromatic carbons than humic acids (2–5 kDa), which in turn have longer-chain fatty acid fragments and therefore possess higher hydrophobicity than fulvic acids. Humic and fulvic acids contain carboxyl substituents in aromatic rings. Their aromatic nuclei have a low degree of condensation and are alternated with parts that are nonaromatic. The presence of conjugated π-electrons in aromatic rings and various functional groups as substituents in combination with the centers of paramagnetic character allow the substances to form complexes, to participate in ionic exchange and oxidation-reduction processes, to react in numerous tautomeric forms—the properties of importance for biological action of these acids. At present, to predict the biological effects of humic and fulvic acids, the corresponding quantitative structure–activity relationships methodologies are applied [Steinberg et al., 2000].

The major functional groups of humic acids are carboxylic, phenolic, and alcoholic hydroxyls, and ketone and quinone groups. That is why fulvic and humic acids are natural metal-complexing compounds [Rouleau et al., 1994]. Thus, crude extracts from mumie, sapropel, and peat are a rich source of microelements. Biological and physicochemical properties of ions are changed dramatically as a result of complexation with humin substances [Senesi and Loffredo, 1999]. The adsorbing capacity of humic and fulvic acids for poisons and mutagen molecules may be a reason for the antitoxic and desmutagenic effects of these acids [Sato et al., 1987; Badaev et al., 1989; Ferrara et al., 2000].

Minor Components of Mumie

Besides humus substances (humin, humic acids, fulvic acids, hymatomelanic acid), mumie contains the following components: albuminoids, amino acids (0.23–0.25%), oxygenated biphenyls, coumarin derivatives (benzocoumarin, dibenzo-α-pyrones), fluorene, mycotoxins (trichothecenes, naptho-l-pyrones, and alternariol), organic acids (benzoic acid and its derivatives, hippuric acid, naphthenic acids), phenolic lipids, polymeric quinines, sterols, tannins, terpenes, and triterpenes [Ghosal et al., 1976; Acharya et al., 1988; Ghosal et al., 1991b]. Mumie is organomineral matter and, according to the results of microelement analysis, it contains (in μg%): Cu (0.02), Zn (0.01), Li (20.0), Al (0.025), Cr (0.001), Pb (0.02), Ag (0.001), Co (0.01), Hg (0.002), P (0.008), Cd (0.05), Br (0.03), V (0.0016), Fe (0.16); Ca (31–39 mM/l), Mg (7.5–10 mM/l), K (100.0–106.6 mEq/l), As, Na, Cl, I, Mn, Mo, S, Si [Mumie liophylisati, 1992; Peerzada et al., 1999]. The structures of some mumie constituents are shown in Fig. 2.

Dibenzo-α-pyrones are capable of permeating through the blood–brain barrier and act as a powerful antioxidant, protecting the brain and nerve tissue from free-radical damage. They also inhibit the enzyme acetylcholinesterase, which breaks down acetylcholine [Schliebs et al., 1997]. This leads an increase of the acetylcholine level. Low levels of acetylcholine are associated with Alzheimer's disease, and poor memory and concentration. The dihydroxybenzo-α-pyrones in mumie cause recycling of ascorbic acid. Mild hydrolysis of humic acids from mumie affords two new dibenzo-α-pyrones: 3-*O*-palmitoyl-8-hydroxydibenzo-α-pyrone and 3-*O*-β-D-glucosyl-8-hydroxydibenzo-α-pyrone, and additionally two new tirucallane-type triterpenic acids: 24(Z)-3 β-hydroxy-tirucalla-8,24-dien-26-oic acid and 24(Z)-3 β-hydroxy-tirucalla-7,24-dien-26-oic acid [Ghosal, 1989].

Mumie contains ellagic and tannic acids, which are natural polyphenolic antioxidants. Tannic acids are stronger inhibitors of superoxide anion radical production by cells than ellagic acid in in vivo and in vitro

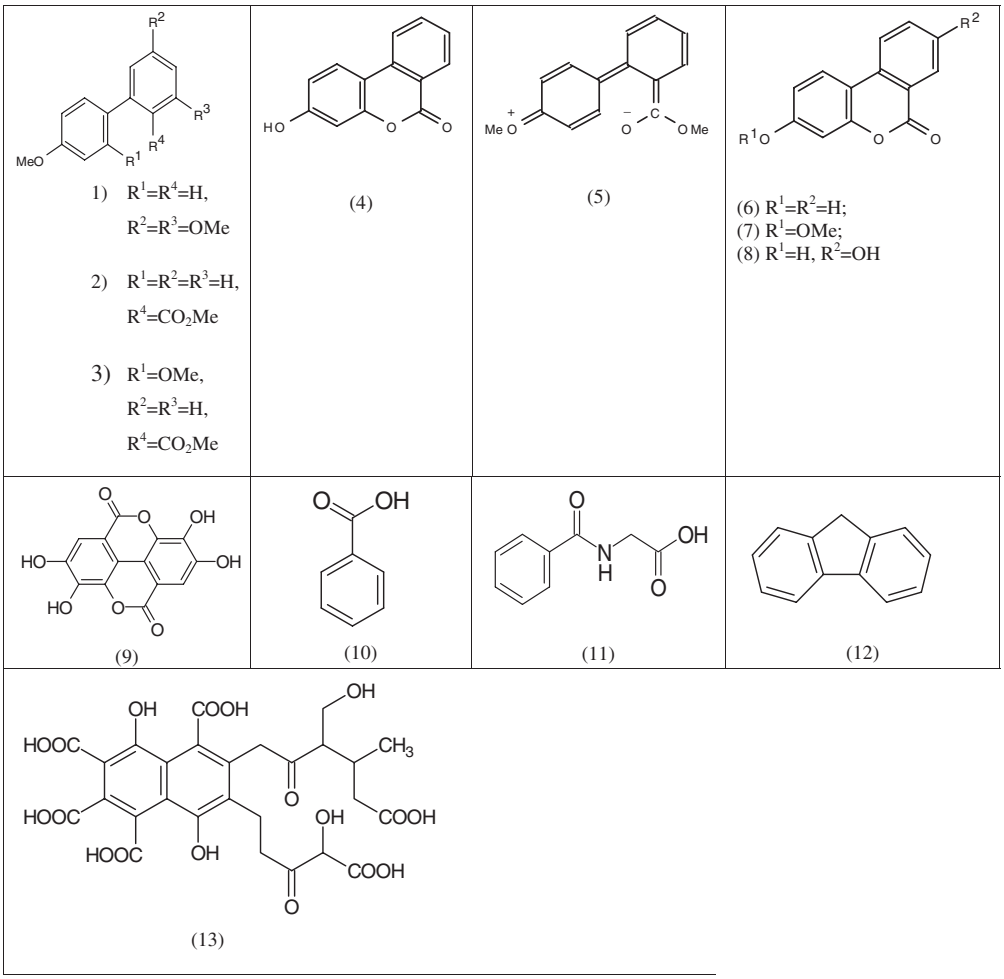

Fig. 2. Some of the compounds that are present in mumie samples: dibenzo-α-pyrones (1–8), ellagic acid (9), benzoic acid (10), hippuric acid (11), fluorene (12), and one of fulvic acids with low molecular weight (model structure by Buffe) (13).

conditions [Kaul and Khanduja, 1998]. Ellagic acid acts as an inhibitor of phospholipase A_2 and an activator of the Hageman factor. This acid is a power anticarcinogenic [Khanduja et al., 1999] and radioprotective [Thresiamma et al., 1998] compound. It induces a downregulation of insulin-like growth factor II, activates p21(waf1/Cip1), mediates a cumulative effect on G_1/S transition phase of the cell cycle, and causes apoptotic cell death of colon cancer cells (SW 480) [Narayanan and Re, 2001].

Some mumie samples contain varying levels of mycotoxins, such as trichothecenes, naptho-l-pyrones, and alternariol [DiCosmo and Straus, 1985]. These mycotoxins may contribute to biological activities of mumie. For example, the trichothecenes can both suppress and stimulate immune function [Bondy and Pestka, 2000].

Medical preparations from peat, sapropel, and mumie may contain halogenated aromatic nuclei as the products of natural degradation of fulvic and humic acids under the action of haloperoxidase enzymes. Some of these organohalogen metabolites demonstrate physiological importance as antibiotics and substances involved in lignin degradation [Dahlman et al., 1993]. The biological effect of halogenated aromatic compounds is mediated by interaction with the Ah receptor [DeVito and Birnbaum, 1995].

CONCLUSION

At present, on the basis of plant natural humification products, pharmacological drugs have been developed that have diverse application in medical practice. These drugs are complex medicines. They can be classified into two groups: (1) extracts and (2) the composites additionally containing extracts from some medicinal plants. The first type of drugs include extracts from peat and sapropel (Torfot, TPP, Peloidodistillate, Humisol, Peloidin, FiBS, Eplir), as well as

extracts from mumie (Mumie, Mumie-Vitas, Shilajit). The second type of preparations include the herbal formulas with mumie (Shilagen, Abana, Cystone, Diabecon 400, EveCare, Geriforte, Lukol, Pilex, Rumalava, Tentex forte, Nefrotec, Adrenotone, Siotone, La-Tone Gold, Andro-Surge, Solanova Libidoplex). Formulations of composite drugs, which include extracts from sapropel or peat, remains so far an undeveloped field in the pharmacology of products from humus material. Extracts from different kinds of humus material have already been applied in folk medicine for several millenniums; nevertheless, only in recent decades has a significant increase in the number of scientific publications been observed, dedicated to the study of extracts from humus material and their mechanisms of action in an organism. One of the problems in the development of the search for new medicines is connected with the difficulty of standardization of multicomponent extracts from humus origin. The modern methods of spectroscopy and identification of organic compounds in the multicomponent organic systems make this problem solvable. It should also be noted that up to now, insufficient attention was paid to the task of isolating individual biological constituents from humus material with the purpose of studying their biological activity. Today, more than 120 distinct chemical substances have been isolated from plants. These substances are considered very important drugs currently in use in one or more countries of the world [Duke, 1990]. The isolation of fractions from unique humificated products of plants for the purpose of detailed study of the pharmacological properties for each group of its constituents seems to be a very promising trend in the development of new drugs. It is reasonable to consider that mumie, as well as peat and sapropel, are very interesting humus materials that also contain unknown substances with high biological activity.

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