ELSEVIER

Herbals in the control of ageing

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The significance of herbals and herbal products is gaining worldwide recognition. The concept of complementary or alternative medicine is becoming much more widely accepted, and there is an increasing belief in the efficacy of herbal remedies. Recently, the role of herbal drugs, herbal products and certain phytochemicals in the control of ageing has been documented using modern scientific approaches. This review pulls together such studies and critiques the efficacy and value of herbal medicines in the control of the ageing process.

Introduction

There is a global resurgence of interest in herbal medicine. The importance of botanicals and herbals is becoming recognised by developed countries. The use of complementary or alternative medicine has increased tremendously in the West, with more and more countries believing in its benefits, which is now regulating and licensing the sale of herbal products into their countries. *Ayurveda* (wisdom of life), the traditional system of medicine in India has its origin in prehistoric antiquity. One of its compilations *Charak Samhita* (~900 BC) lists 10 anti-ageing drugs. Of these, seven are also plants that are used in *Rasaayan* (rejuvenation) therapy [1]. Those herbal drugs purported to possess anti-ageing properties have been subjected to modern scientific investigation and have been found to have significant free radical quenching and other antioxidant properties. Plants and plant products, including certain phytoconstituents and their modified forms, which form the basis of anti-ageing regime [2], are discussed within this review. We include a non-exhaustive list of some of the most significant herbal approaches to the treatment of the symptoms of ageing, a diverse list of conditions involving biophysical changes to bone and skin, cardiovascular change (such as hypertension), mood and cognitive disorders, connective tissue problems, cancer, diabetes and general vitality. As might be expected, and has just been mentioned, many work through their ability to act as antioxidants or free radical sinks. Others, however, appear to have novel and unique actions against very specific pathways.

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Herbal drugs

Throughout this review, the structures of those compounds that have been numbered in the text are given in Figure 1.

Aloe

The leaves of *Aloe vera* (*A. barbadensis*) (Fam. Liliaceace) are the source of aloe vera gel. The gel does not include the sap of *Aloe vera*, which contains anthraquinones. *Aloe vera* gel is widely used in cosmetics and toiletries for its moisturizing and revitalizing action. The organic whole leaf of *Aloe vera* is reported to aid in cellular repair and in digestion, assimilation of foods, vitamins, minerals and other vital nutrients [3–5].

Ashwagandha

Ashwagandha, an herbal drug from the Indian system of medicine, consists of the dried roots of *Withania somnifera* (Fam. Solanaceae). Leaves and stem bases are also included in such preparations. It is commonly referred to as Indian Ginseng. It is reported to have anti-infective, antitumor, anti-stress, antioxidant, mind-boosting, rejuvenating and anti-ageing properties. It contains flavonoids and withanolides. The antioxidant effect is due to natural antioxidants, superoxide dismutase, catalase and glutathione peroxidase, which account for many of its other effects. Reports of cognition-enhancing properties are likely to be due to increased

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2009.06.014

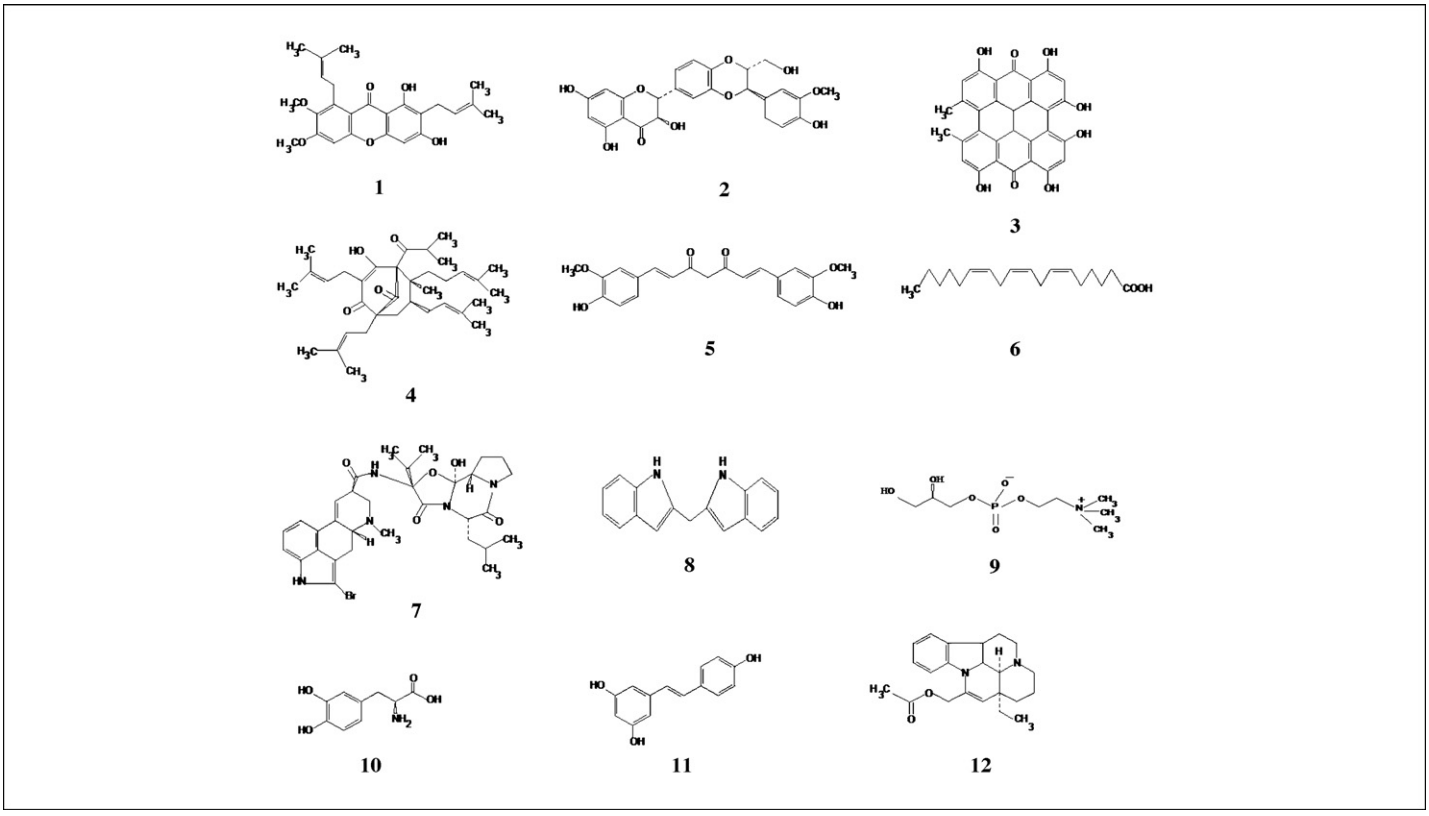

FIGURE 1

Herbal compounds with activity in the control of ageing.

cholinergic activity and its GABA-like activity may also promote anxiolytic effects [6–9].

Brahmi

Brahmi buti, *Bacopa monnieri* (Fam. Scrophulariaceace) is a classic brain and nerve tonic used for the treatment of cognitive disorders of ageing. It helps to improve protein activity and protein synthesis, especially in brain cells, which can impact congnition, and memory and decrease senility [10,11]. The plant contains the alkaloids brahmine and herpestine, and saponins.

Cat's claw

The bark of *Uncaria tomentosa* (Fam. Rubiaceae) popularly known as cat's claw bark is used as an immunostimulant and might help in the prevention of colds, flu, bacterial and fungal infections, cancer and arthritis [12]. Cat's claw also acts as an antihypertensive [13].

Cinnamon

Cinnamon is the dried bark of the shoots of *Cinnamomum zeylanicum* (Fam. Lauraceace). The bark yields a volatile oil that is rich in cinnamicaldehyde. The powdered bark is reported to regulate blood sugar levels (just a half spoon daily yielded a 20% drop in blood sugar), reduce inflammation and prevent growth of bacteria and fungi in the body. Its smell in itself may be sufficiently potent to enhance memory, learning and visual-motor speed [14–17].

Echinacea

Echinacea, the dried rhizome and roots of *Echinacea purpurea* (Fam. Compositae) and other species, such as *E. angustifolia*, *E. pallida*, or the aerial parts of *E. purpurea*, is reported to have immunostimulant properties. The roots contain phenolic components and the aerial parts contain chicoric acid and isobutylamides of dodecatetraenoic acid. Echinacea is widely used to treat the common cold and upper respiratory tract infections [18,19].

Emblica

The extract from the plant *Phyllanthus emblica* (*Emblica officinalis*) (Fam. Euphorbiaceae) is reported to reduce free radicals that contain trigalloyl glucose and tannins [20].

Ginkgo

Ginkgo consists of the whole or fragmented dried leaf of *Ginkgo biloba* (Fam. Ginkgoaceae). It is a popular herb used for improved memory functions. Ginkgo stimulates blood flow to the brain by dilating blood vessels and decreasing platelet aggregation. Being a powerful antioxidant, it blocks the oxidation of the fatty cell membrane. Ginkgo has been shown to help slow down Alzheimer's disease [21–24].

Ginkgo biloba (leaves) generally contains approximately 24% flavonglycosides primarily composed of quercetin, kaempferol and isorhamnetin, and 6% terpene lactones, such as ginkgolides A, B and C and bilobalide. Other constituents include proanthocyanadins, glucose, rhamnose, organic acids like hydroxykinurenic, kinurenic, protocatechic, vanillic and shikimic acids. D-Glucaric acid and ginkgolic acid, and related alkylphenols, are also present.

Ginseng

Ginseng is the dried root of *Panax ginseng* (Fam. Arabiaceae), known as Asian ginseng. Other species of ginseng are *P. quinque-*

folius (American ginseng) and *P. pseudoginseng*. Ginseng contains a complex mixture of soponins termed ginsenosides or panaxosides. Extracts of the roots of *P. ginseng* are reported to yield around 13 saponins. Ginseng is reported to enhance natural resistance and the recuperative power of the body and to reduce fatigue. It is commonly known as adaptogen, which helps combat stress and regulate the immune system. It prevents colds, flu and is effective in lowering sugar and cholesterol levels in the blood. It is also found to be effective in the treatment of some forms of cancer [25].

Green tea

The leaves of *Camellia oleifera* (Fam. Theaceae), when used as infusion, act as an antioxidant and skin rejuvenator owing to presence of polyphenolic compounds—catechins and epicatechins [26–29]. It has been shown to inhibit genes that drive breast cancer and also to reduce the risk of cardiovascular disease [30,31]. There are a number of reports on skin photoprotection by polyphenolic antioxidants of green tea [32,33], which has been excellently reviewed by Ahmad *et al.* [34].

Hawthorn

The dried tips of the flower-bearing branches of *Crataegus monogyma* (*C. laevigata*, *C. oxycanthus*) (Fam. Rosaceae), commonly known as hawthorn berries, are reported to have activity useful for the treatment of coronary disease, angina, sleep disorders and dilate blood vessels [35]. The drug contains the C-glycosylated flavones, vitexin and hyperoside.

Horse chestnut

Horse chestnuts are the seeds of *Aesculus hippocastanum (A. indica)* (Fam. Hippocastanaceae), which are used as food, feed and fodder, and for the production of alcohol. They have been used in human and veterinary medicines for the treatment of fevers, haemorrhoids, obstinate constipation, mammary induration and cancer [36]. The meal of horse chestnuts is employed to cleanse oily skin. Owing to their saponins content, the seeds possess toxic properties. Alcoholic extracts of seeds of *A. hippocastanum* show haemolytic, antioedema and other pharmacological properties. Extracts have been also applied in cosmetics, whereas the oil extracted from *A. indica* seeds exhibits a significant anti-inflammatory activity in carrageenin-induced oedema in rats. Seed oil contains 65–70% oleic acid.

The two most important active components of the chestnut have been identified as aesculin, which is a coumarin derivative, and aescin, a saponin. In addition there are a number of flavones. Aescin is a mixture of triterpene saponins and is the main bioactive constituent of horse chestnut seeds, twigs, sprouts and leaves. It exhibits potent anti-inflammatory activity, reduces capillary fragility and, therefore, helps to prevent fluid exudation that causes swelling into surrounding tissues [37]. Horse chestnut extract was also found to have a more potent anti-oxidant activity than Vitamin E. Among 65 plant extracts tested, horse chestnut extract was shown to have one of the highest 'active-oxygen' scavenging abilities and exhibited a potent cell protective effect. These activities are linked with some of the anti-ageing properties of antioxidants [38,39]. The extract is also rich in a number of flavonoids, such as derivatives of quercetin and kaempferol. Flavonoids also have exert protective effects on blood vessels and are well known, powerful antioxidants.

Horse chestnut extract is reported to have beneficial effects on venous insufficiency and associated conditions. Aesculin is used in preparations for the treatment of peripheral vascular diseases, haemorrhoids and cosmetics designed to ameliorate ageing skin [40,41].

Kava-kava

Kava is the rhizome of *Piper methysticum* (Fam. Piperaceae), a shrub indigenous to South Pacific. Pyrone derivatives, such as kawain, methysticin and yangonin, are its major constituents. The drug is attributed with sedative, skeletal muscle relaxant and anaesthetic properties; it is reported to have central nervous system depressant effects, to produce euphoria, reduce anxiety and enhance sleep [42,43].

Mangosteen

Mangosteen is the edible fruit obtained from *Garcinia mangostana* (Fam. Guttiferae). The fruit rind (pericarp) extract contains xanthones (mainly *alpha*-mangostin and *gamma*-mangostin) (1). These are phytonutrients that exhibit strong antioxidant activities and enhance and support the body's immune system [44].

Maritime pine

The bark of the maritime pine, *Pinus pinaster* (Fam. Pinaceae) is a source of a mixture of proanthocyanidins known as pycnogenol. It is a potent antioxidant capable of protecting the liver from free radical attack. Since the liver is the main detoxifying, nutrient-assimilating, and energy-generating organ of the body, this may mean more potential for activity in life. It prevents collagen destruction and thus restores the strength of capillaries and improves circulation, making it easier in treating the capillary fragility of ageing skin [45,46].

Milk thistle

Milk thistle, *Silybum marianum* (*Cardius marianus*) (Fam. Compositae) fruit contains silymarin, a mixture of flavolignans including the isomer silybin, silicristin, and silidianin, of which silybin (2) is the major component. Silymarin is claimed to be a free radical scavenger and has hepatoprotective properties. The fruit extract may help slow the extent of diabetic retinopathy, which is the major cause of blindness among adults in the developed world. It reduces lipoperoxidation of cell membranes and insulin resistance, significantly decreasing endogenous insulin overproduction and need for exogenous insulin administration. It also prevents from ultraviolet radiation induced DNA damage and thus protects skin [47–50].

Passion flower

Passion flower is the common name of fragmented or cut, dried aerial parts of *Passiflora incarmata* (Fam. Passifloraceae). One of the major components of the preparation is the flavonoid vitexin, which is reported to have sedative properties. It also has been claimed to act as an antispasmodic, an antiasthamatic and an aphrodisiac [51–55].

Pygeium

Pygeium consists of the bark of *Prunus africanum* (*Pygeium africanum*) (Fam. Rosaceae). The extract of the bark can relieve the symptoms of benign prostatic hyperplasia (BPH). Pygeium extract

contains phytosterols, terpenes and ferulic esters. These constituents have demonstrated anti-inflammatory effects and anti-oedema (anti-swelling) effects in the prostate gland [56,57].

Saw palmetto

Saw palmeto is the dried fruit of the American dwarf palm, *Serenoa repens* (Fam. Arecaceae). Saw palmeto is mainly used as a crude extract of fruits, which are highly enriched with fatty acids and phytosterols. This herb has been shown in many studies to help relieve the common symptoms of BPH, a common problem associated with most males over 35–40 years of age, with symptoms such as urination frequency, difficulty in passing urine, and a decrease in the force of the urine stream due to restriction of the urethra by the hypertrophic prostate gland. The herb works by multiple mechanisms, including inhibiting 5-alpha-reductase, interfering with dihydrotestosterone binding to the androgen receptor, by relaxing smooth muscle tissue (in a similar fashion to alpha antagonist drugs) and possibly by acting as a phytoestrogen [58,59]. It has also been used as an herbal treatment for baldness. While saw palmetto is generally considered safe, one of its primary active ingredients, β-sitosterol, is chemically similar to cholesterol. High levels of sitosterol concentrations in blood have been correlated with increased severity of heart disease in men who have previously suffered from heart attacks.

St. John's wort

St. John's wort is the dried flowering tops or aerial parts of *Hypericum perforatum* (Fam. Hyperiaceae) gathered before or during flowering. The preparation contains hypericin (3), its isomer pseudohypericin and hyperforin (4). St. John's Wort has value in the treatment of depression and anxiety associated with ageing [60,61].

Stinging nettle

The preparation uses the dried roots and rhizomes of *Urtica dioica* (Fam. Urticaceae) but may also contain *U. urens*, known commercially as dwarf nettle, in small amounts. Urtica is used mainly for rheumatic and urinary disorders. It is reported to be used as a natural agent to reverse trends of prostate enlargement [62,63].

Turmeric

The dried rhizome of *Curcuma longa* (Fam. Zingiberaceae) in its powdered form, is referred to as turmeric, is used commonly as a main constituent of curry powders. Turmeric and its main constituent curcumin (5) have been shown to have cytoprotective effects through its hormetic anti-ageing action in stimulating the synthesis of heat-shock proteins [64].

Valerian

Valerian consists of subterranean parts of *Valeriana officinalis* (Fam. Valerianaceae), including the rhizomes, roots and stolons. It contains the volatile oil, valerinic acid and its epoxy-iridoil esters, collectively known as valepotriates. The preparation has sedative properties and is used for the treatment of anxiety states [65–67]. Valerian oil is also used in aromatherapy.

Shilajit

Shilajit is a thick paste oozing from the rocks of Himalayan mountains. It has since ancient times been claimed to have unmatched powers of arresting and reversing the ageing process. Shilajit (mineral pack) contains more than 85 minerals in ionic form and fulvic acid, humic acid, hippuric acid and benzopyrones. Humic acid assists fulvic acid in its action and, in combination with benzopyrones, also exhibits antioxidant effects. Hippuric acid can have beneficial effects in genito-urinary conditions. Shilajit acts as a powerful aphrodisiac and restorer of vitality [66]. Shilajit is also reported significantly to reduce the chances of developing degenerative ailments like cancer, diabetes, heart disease, osteoporosis, joint pains and dementia [67]. It can also help in controlling weight [68].

Herbal products and phytochemicals

Biostim

Biostim is the proprietary name for the glycoproteins extracted from bacteria *Klebsiella pneumoniae*, is a potent immune system stimulant that boosts phagocytosis, humoral reactions and cellular immunity [69]. It is also used in the management of respiratory tract infections.

Borage oil

Borage oil is obtained from the seeds of *Borago officinalis* (Fam. Boraginaceae). Borage (starflower) oil delivers gamma-linolenic acid (6) (GLA) to cells for membranes, which produces beneficial effects on skin [70,71]. Delta-6-desaturase (D6D) is essential for synthesis of GLA from linoleic acid in the body. Borage oil can circumvent impairment in D6D (due to various skin diseases associated with ageing) by supplying the body directly with GLA. This is further converted, via a sequence of biochemical steps, into a very important compound called prostaglandin$_1$ (PG1), a key molecule for maintaining healthy skin. PG1 exhibits a potent anti-inflammatory effect on the skin and also is very effective in regulating water loss and protecting skin from injury and damage.

Diindolylmethane

Diindolylmethane (7) (DIM) is a phytonutrient found in broccoli, cauliflower, cabbage and brussels sprouts that balances oestrogen levels, promoting health and well being. It helps to regulate and promote a more efficient metabolism of oestrogen and an optimal ratio of oestrogen metabolites. It works indirectly by increasing the activity of enzymes that control oestrogen production. DIM boosts levels of 'good' oestrogens called 2-hydroxyoestrogens and reduces levels of 'bad' oestrogens that are 16-hydroxy and 4-hydroxyoestrogens. Both forms of 'bad' oestrogens are carcinogens. It also reduces the risk of breast cancer in women and prostate cancer in men [72].

Equistat

Equistat is composed of apple and soyabean extracts in a non-aqueous butylene glycol vehicle. The apple extract contains terpenoid compounds, such as ursolic acid, which are proven inhibitors of elastase and possess anti-inflammatory and collagen stimulatory activities. Peptides of the soya hydrolysate, in combination with the soya isoflavones-genistein, daidzein and their glycosides and the apple triterpenes, act synergistically as matrix metalloprotease inhibitors. Ursolic acid helps to reduce the appearance of wrinkles and age spots by restoring the skin's collagen structure and elasticity. Genistein and daidzein stimulate hyaluronic acid production in skin cells [73,74].

Ergoloid mesylates

Ergoloid mesylates (dihydroergotoxine monomethane sulphonate) is a mixture of methane sulphonic acid salts of dihydroergocornine, dihydroergocristine and α-and β-ergocriptine. Available under the proprietary name of hydergine presents itself as a remarkable anti-ageing medicine and an adjunct in the treatment of age-related mental decline. It mimics nerve growth factor (NGF), and is a powerful antioxidant capable of delaying brain death in cases of heart failure and stroke by several minutes with regular use. It increases vigilance [75,76].

A mention can be made of bromocriptine (8), a semi-synthetic derivative of the ergotoxin group of ergot alkaloids. Its first major anti-ageing use is the enhancement of dopamine (a key brain neurotransmitter that undergoes an age-related decline). Its second major anti-ageing effect is the inhibition of prolactin synthesis. This hormone is one of the few that actually appears to increase with age and trigger lactation and weight gain in pregnancy and also acts as an immunosuppressant. Bromocriptine has been used to help restore ovulation in women. In addition, it acts as a very potent free radical quencher and is effective in the treatment of breast cancer and type-2 diabetes [77].

L-α-Glycerylphosphorylcholine (L-α-GPC)

Also known as choline alfoscerate (9), L-α-GPC helps to boost acetylcholine levels. It aids in the synthesis of several brain phospholipids, which increases the availability of acetylcholine in various brain tissues. It helps protect against the cognitive decline normally seen in ageing. It increases human growth hormone (HGH) and *gamma*-aminobutyric acid (GABA) release. GPC also increases the release of the dopamine, a chemical messenger in the brain that regulates emotions, sensation of pain and pleasure and physical movement. This may be useful in the treatment of Parkinson's disease [78,79].

Levodopa

Levodopa (10) (L-dopa) occurs naturally in broad beans or *Vicia faba* (golden beans) and is a drug used in the treatment of Parkinson's disease. There is a direct biochemical relationship between the age-related decline of serotonin and lower levels of L-dopa. Deficiency of L-dopa leads to growth hormone deficiency, resulting in slowness of movement and speech and cognitive impairment [80,81].

Phytooestrogens

These are plant oestrogens or isoflavones present in legumes, soyabean, flax seeds, black cohosh and red clover extract. They mimic the action of oestrogen, but have a much weaker effect. This makes them useful in the treatment of osteoporosis. They help balance oestrogen levels and keep the skin healthy. They also reduce the risk of prostate cancer in men [82,83].

Resveratrol

Resveratrol (11) is a phytoalexin (a protective compound produced by plants in response to environmental stresses) present in a number of plants, such as species of *Arachis*, *Pinus*, *Polygonum*, *Veratrum* and *Vitis*. Commercially, resveratrol is obtained from the roots of Japanese knotweed *Fallopia japonica* (Fam. Polygonaceae). Resveratrol, as a mixture of *Z* and *E* isomers, has anti-inflammatory, antioxidant, anti-infective properties and can protect the cardiovascular system. It has promising therapeutic activity in various cancers, including breast, prostate and neuroblastoma. It has potent antifungal and anti-influenza activity. It is hypothesized that resveratrol, a red wine polyphenol, may be responsible, partly, for the health benefits of moderate red wine consumption on retinal disease (age-related macular degeneration) owing to its antioxidant and antiproliferative effects [84–89].

Vinpocetine

Vinpocetine (12) is a derivative of vincamine, the major indole alkaloid of *Vinca minor* (Fam. Apocyanaceae). It has been shown to cause circulatory and metabolic enhancement in brain through its cholinergic actions and prevent free radical damage in brain cells and also raise brain levels of serotonin [90]. It is a recommended therapy for acute ischaemic stroke.

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