



Synthetic drugs with anti-ageing effects

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Although ageing is a natural wear and tear phenomenon, it can at least be postponed or prevented by certain approaches. Some chemicals that are present in the diet or in dietary supplements have been documented to have anti-ageing effects. Recently, a number of synthetic drugs used for other therapeutic indications have been shown to have anti-ageing potential.

Ageing, or senescence, commonly known as the process of getting old is a combination of processes of deterioration that follow the period of development of an organism. Cellular senescence [1] refers to the loss of a cell's ability to divide and grow. Ageing is characterized by a number of symptoms, such as a declining ability to respond to stress, increasing homeostatic imbalance and increased risk of disease, wrinkling of skin due to loss of fat and increased degradation by matrix metalloproteinases (MMP) and reduced synthesis of its extracellular matrix (principally collagen and elastin) [2]. Degeneration of neurons, which in the main are not replaced result in progressive cognitive loss, possibly even resulting in dementia. Death is the ultimate consequence of ageing.

Biochemical changes taking place in ageing include damage to biopolymers, such as proteins or DNA by oxygen (as free radicals) and by sugars, such as glucose and fructose; the former called oxidant damage and the latter as non-enzymic glycation [3]. An unhealthy life style, poor eating habits, smoking, excessive alcohol consumption, stress and depression potentiate the process of ageing [4–12].

Although ageing is a natural wear and tear phenomenon and bodily decay is an inexorable process, ageing can at least be postponed or prevented by certain approaches. Though somatic treatment of ageing is still a far-fetched goal, recent investigations have shown that there are a number of chemicals derived from nature, in addition to a number of synthetic drugs, with varied therapeutic effects that may be useful in the control of the process of ageing.

Natural products with reported anti-ageing effects

A number of natural products (see Figure 1) with widely differing chemical structures have been reported to exert their anti-ageing effects through varied mechanisms. These are briefly discussed below.

β -Carotene (**1**) is a precursor of vitamin A; it has antioxidant activity and has been studied for its protective properties in a number of age-related disorders [13,14].

Lycopene (**2**) is present in high concentrations in tomatoes and has been claimed to provide protection against many diseases, including cardiovascular diseases and some cancers, particularly prostate and is capable of directly blocking ultraviolet rays [15,16].

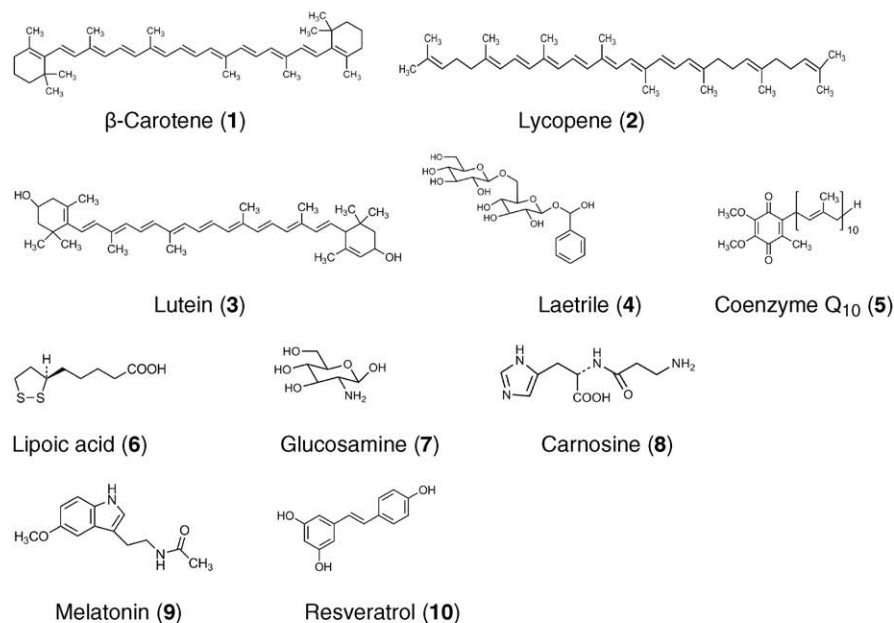
Lutein (**3**), present in vegetables and fruits decreases the chances of developing macular degeneration [17].

Laetrile (amygdalin; vitamin B₇; chemically laevo-mandelonitrile-glucoside), commonly found in apricots (**4**), is a powerful hydroxyl radical scavenger. This property underpins the rationale for its role in anti-ageing supplement programs [18,19].

Coenzyme Q₁₀ (CoQ₁₀; ubedecarenone) (**5**) acts as an antioxidant and improves both rate and efficiency of energy production in cells [20].

Lipoic acid (ALA; thioctic acid), chemically 5-(1,2-dithiolane-3-yl)valeric acid (**6**) is a potent antioxidant and anti-crosslinking agent; it is purported to reduce hardening of arteries, wrinkling of skin and stiffening of joints [21].

Glucosamine (**7**) acts as an important nutrient supplement for old people as it stimulates manufacture of glycosaminoglycans, important components of the cartilage needed for healthy joints [22].



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FIGURE 1

Natural products with anti-ageing effect.

Carnosine, chemically β -alanyl-L-histidine (**8**), is a naturally occurring dipeptide found in large amounts in skeletal muscle and also in brain, cardiac muscle and kidney. It acts as an antioxidant, an anti-crosslinking and anti-glycating agent and protects against cataracts and neurodegeneration [23].

A mention may be made here of a synthetic tetrapeptide, Epitalon, which has been found to have an anti-aging profile associated with pineal gland products, such as melatonin. It is reported to induce telomerase activity and telomerase elongation in human somatic cells [24,25]. Melatonin (**9**) has been shown to have a range of anti-ageing effects, including regulation of reproductive function, suppression of certain types of tumours and effects on mitochondrial function [26].

Resveratrol (**10**) is a phytoalexin present in a number of plants. This polyphenol is also present in red wine and appears to be beneficial in protecting against age-related macular degeneration, possibly through its antioxidant, anti-proliferative properties [27–32].

Synthetic drugs with anti-aging activity

Recently, a number of synthetic drugs (see Figure 2) used in a variety of therapeutic indications have been reported to have anti-ageing effects.

Aspirin

One of the most common causes of disability and death can arise from blood clots that develop inside a vessel. When dislodged, they may cause heart attack, or stroke. Aspirin (acetylsalicylic acid) (**11**) is an analgesic, antiinflammatory and antipyretic drug. It acts through inhibition of cyclooxygenase, the enzyme responsible for synthesis of prostaglandins and thromboxanes from arachidonic

acid. Aspirin inhibits platelet aggregation and has an immediate and long-lasting effect on blood platelets, making them less likely to clump, hence reducing the risk of further clots. It is reported that aspirin delays the onset of endothelial senescence by preventing reduction of NO formation/generation and has also been found to inhibit senescence-associated β -galactosidase activity and increased telomerase activity [33,34].

Doxycycline

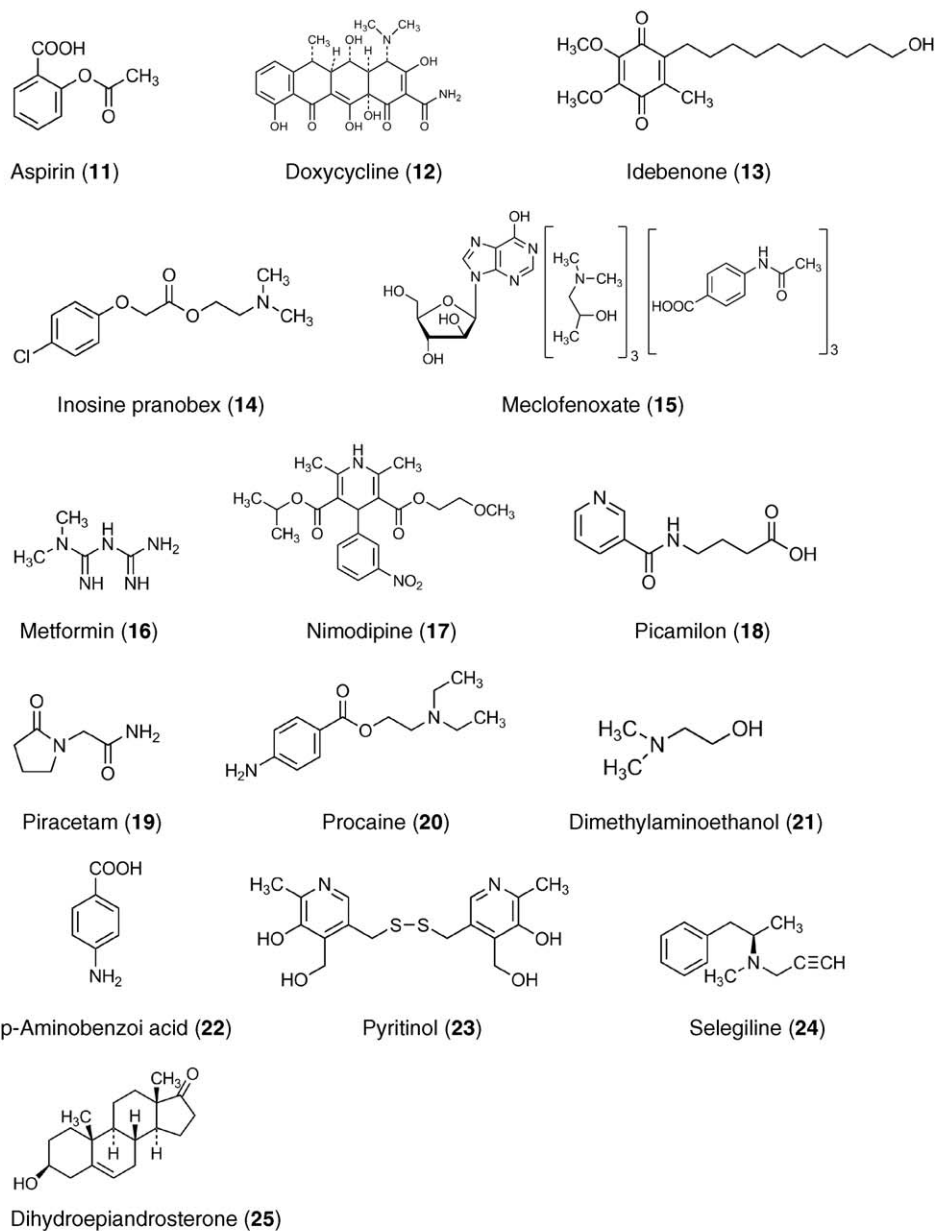
Doxycycline (**12**) is a derivative of tetracycline that retains antibacterial properties. Doxycycline hyclate (hydrochloride hemiethanolate hemihydrate) is reported to act as a skin rejuvenator through inhibition of matrix metalloproteinases (MMP). Its use was established in periodontal disease, where it is thought its action on connective tissue helps strengthen the gums. So theoretically, it may help to treat wrinkles if used topically, but studies are needed to determine safety and efficacy of such use [35–37].

Idebenone

Idebenone (**13**), a benzoquinone closely structurally related to CoQ₁₀, is a potent agent in the treatment of wrinkles. It acts as an antioxidant and is more soluble than CoQ₁₀. It can perform the same functions as CoQ₁₀, but without autooxidation [38,39].

Inosine pranobex

Inosine pranobex (**14**) (isoprinosine) is an immunostimulant complex formed from the *p*-acetamidobenzoate salt of dimethylaminoisopropanol and inosine in a 3:1 molar ratio. It has antiviral properties and is reported to restore immune responses in ageing humans [40].



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FIGURE 2

Synthetic drugs in therapeutic use that also have purported anti-ageing effects.

Meclofenoxate

Meclofenoxate (**15**) (centrophenoxine) Centrophenoxine's possible anti-ageing benefits include protection against free radical damage in the brain, increased potential lifespan, reduction and prevention of age spots on the skin, increased mental energy, improved memory and learning ability, and prevention and treatment of stroke and brain injury. Animal studies have found that centrophenoxine is effective at removing lipofuscin (potassium age pigment) from the brain, heart, and skin [41]. It has generally been prescribed for the treatment of cognitive deficits in the elderly. It is an agent with similar effects on learning and memory to vinpocetine and hydergine [42].

Metformin

Metformin (**16**) is an antidiabetic drug, which works through enhancing the sensitivity of cell surface insulin receptors of muscle and fat cells to insulin involved in gluconeogenesis in the liver and thus reduce the risk of glycation and other age-related damage [43,44].

Metformin also modulates stress responses through activation of adenosine monophosphate-activated protein kinase (AMPK) that exerts its effect through switching on pathways capable of preventing and repairing cell damage by producing a sudden bout of energy production concomitant with suppressing those energy-demanding processes not directly essential for the survival of the

organism [45]. This is exactly what happens during calorie restriction when the body is in 'survival mode' and when nutritional stress of a low calorie diet activates pathways that increase cell repair. Therefore, metformin can act as a calorie restriction mimic [46].

Nimodipine

Nimodipine (**17**), a dihydropyridine calcium L channel blocker developed for the treatment of high blood pressure. Nowadays, it is not generally used for this indication, but is frequently used for the treatment of vasospasm, a major complication of subarachnoid haemorrhage [47,48].

Picamilon

Picamilon (**18**) is a proprietary name for sodium *N*-nicotinyl- γ -aminobutyrate, and structurally it is a combination of GABA and niacin. It appears to be more effective than either hydergine or vinpocetine in improving blood flow in cerebral vessels that, in turn, produces cognitive enhancement. This effect is due to the synergy between the niacin and GABA molecules present in the hybrid structure, which readily crosses the blood brain barrier where it protects neurons against the effects of diminished oxygen during neurological ageing [49–51].

Piracetam

Piracetam (**19**), chemically 2-(2-oxopyrrolidin-1-yl)acetamide, is a nootropic that protects cerebral cortex from hypoxia, perhaps through enhancing blood flow. It increases the sensitivity of receptors in the brain involved in memory and learning and, hence, may help to slow down brain ageing [52].

Procaine

Procaine (**20**) is a local anaesthetic, used in the treatment of arthritis and pain conditions. It reduces depression and provides a feeling of greater vitality and youthfulness. Procaine, however, has a stability problem and it rapidly hydrolyses in the body and remains active only for a comparatively short time. In order to improve its effect, a combination of procaine with benzoic acid as a preservative, and potassium metabisulfite as an antioxidant is used under the name of Gerovital H₃ (GH₃). Another combination, named Aslavit, has pyridoxine (vitamin B₆), mesoinositol and glutamic acid further supplementing those additives found in GH₃. Aslavit is reported to have an even more powerful and beneficial effect on memory, atherosclerosis and other degenerative conditions than the original Gerovital H₃ [53].

Gerovital H₃ (GH₃) also appears to be a relatively safe, yet weak MAO inhibitor and represents a major advance in the field of anti-ageing [54]. Procaine, as Gerovital H₃ and Aslavit, has numerous documented mechanisms of action. These include inhibition of monoamine oxidase (an enzyme in the brain that increases with age); nootropic properties and antioxidant action [55]. It can be a useful adjuvant to other longevity agents and may be able to potentiate their effectiveness. When procaine enters the body, it is broken down into *para*-aminobenzoic acid (PABA), and diethylaminoethanol (DEAE), both of which are naturally present in the body. Both of these substances are biologically active and have numerous beneficial effects of their own. Although the majority of the research involving Gerovital and Aslavit attributes the ben-

efits to the procaine molecule itself, there is still controversy as to whether the effects are due to procaine molecule itself, or its metabolites, PABA and DEAE [56,57].

Dimethylaminoethanol (**21**) (deanol; DMAE), an analogue of DEAE, is a precursor of choline and is a naturally occurring nutrient found in foods such as anchovies and sardines. It stimulates the production of choline, which, in turn, allows the brain to optimize production of acetylcholine. Acetylcholine is the primary neurotransmitter involved in learning and memory. DMAE inhibits the formation of ageing pigment (lipofuscin) and flushes it from the body. Lipofuscin is believed to be formed by the inefficient metabolism of fatty acids, and it accumulates with age in all body tissues, acting as intracellular garbage [58]. Dimethylaminoethanol supposedly also has a positive effect on periorbital oedema (swelling of the eyelids) and on skin tightness [59]. *p*-Aminobenzoic acid (**22**) (PABA) has been used as a component of many commercially available sunscreens, due to its ability to block damaging ultraviolet rays. PABA, both topically and orally, is truly an anti-ageing substance with respect to its ability to protect skin from the sun [46]. This versatile substance also has the potential to restore hair to its natural colour and encourage hair regrowth [60]. PABA also acts as an antioxidant, protecting cellular membranes and mitochondrial DNA from free radical attack and oxidative stress. With respect to its other actions on ageing, it also acts as an anti-crosslinking agent by slowing and, in some cases, even reversing crosslinking in connective tissue proteins, such as collagen, and thus may enhance flexibility in normally ageing individuals [61].

Pyritinol

Pyritinol (**23**) promotes the uptake of glucose by the brain. It is used in the treatment of various cerebrovascular and mental disorders. It produces an even more pronounced enhancement of cognitive function than ergolines and has been used for the treatment of a wide variety of neurologic disorders [62,63].

Selegiline

Selegiline (**24**) (deprenyl), an antiparkinsonian drug, is an irreversible inhibitor of monoamine oxidase type B, an enzyme involved in the metabolic degradation of dopamine. Inhibition of the enzyme thereby elevates dopamine levels in the brain and central nervous system. In addition to its use as a drug for Parkinson's Disease, it has also proved clinically useful for the treatment of depression and dementia. Selegiline is also noteworthy for its ability to upregulate antioxidant enzyme activities while simultaneously suppressing hydroxyl radical formation in the *Substantia nigra* [64–67].

Hormone replacement therapy

It is felt that a significant contribution to the ageing process resides in the hormonal profile of individuals, especially those hormones that peak around early adulthood then taper off with age, such as sex hormones, the human growth hormone (HGH) and the pineal hormone, melatonin. One of the latest additions to this list is the adrenal cortex steroid hormone, dihydroepiandrosterone (**25**) (DHEA), HGH, testosterone and melatonin supplementation improve overall vitality, that is, strength, vigour and muscle mass and increase mobility and restful sleep and produce less joint pain and can induce a psychological sense of well-being [68,69].

DHEA has anti-ageing potential as great, or even greater, than other hormones [69,70]. It has a better side effect liability and is easy to administer in tablet form and is some 20–25 times cheaper than synthetic HGH, which has to be injected twice daily.

The anti-stress, immunoenhancing, neuroprotective and cardiovascular benefits of DHEA have established its potential in any anti-ageing protocol [69,70].

Hormone replacement therapy (HRT) helps women age gracefully, reduces age-related debility and ailments and helps to ameliorate perimenopausal symptoms. The decline in oestrogen concentrations in menopausal woman may represent both acute and long-term effects, some of which may resemble the accelerated effects of ageing. Such a situation may be managed by hormone replacement therapy (HRT) using oestrogens, with or without progestogens. It results in more youthful appearance and some health benefit. Oestrogen is prescribed to postmenopausal

women to combat the symptoms of depression and osteoporosis among others. Progesterone is a growth hormone stimulant capable of stimulating the breakdown of fat and evidence suggests that it may be able to protect against endometrial cancer when given with oestrogen for 10 or more days *per cycle* [71,72].

Testosterone replacement therapy (TRT) for men is as potent in its anti-ageing effects as oestrogen and progesterone are in women [73].

Conclusions

A number of chemical substances present in our diet or dietary supplements have already been documented to have anti-ageing effects. Recently, studies have shown that a number of synthetic drugs used therapeutically for other indications may have properties that can prevent or postpone the process of ageing. The results are striking and warrant further research.

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