CHAPTER

3

Amla in the Prevention of Aging: Scientific Validation of the Ethnomedicinal Claims

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3.1 INTRODUCTION

Phyllanthus emblica (syn. *Emblica officinalis*), commonly known as the Indian gooseberry in English, is arguably the most important medicinal agent in the traditional Indian system of Ayurvedic medicine [1,2]. It is colloquially known as amla or amlaki in most Indian languages (Table 3.1). The plant, which belongs to the family Euphorbiaceae and was originally indigenous to India, is today also found growing in other tropical countries like Pakistan, Uzbekistan, Sri Lanka, China, and Malaysia, and other areas in Southeast Asia [3]. The fruits (also known as the berries or myrobalans) are the most important plant part, and are of dietary, culinary, and medicinal use (Figure 3.1). The fruits of amla are an important dietary agent and are used to make murabbah, burfi, ladu, fresh juice, pickle, chutneys, and curries in India [4].

Amla is a rich source of vitamin C, and reports indicate that levels of this crucial vitamin in amla are greater than in oranges, tangerines, or lemons [5]. The other important constituents of amla are gallic acid, ellagic acid, chelubic acid, chebulinic acid, chebulagic acid, emblicanin-A, emblicanin-B, punigluconin, pedunculagin, citric acid, ellagotannin, trigallayl glucose, pectin, 1-O-galloyl-β-D-glucose, 3, 6-di-O-galloyl-D-glucose, corilagin, 1, 6-di-O-galloyl beta-D-glucose, 3-ethylgallic acid (3-ethoxy-4,5-dihydroxybenzoic acid), and isostrictiniin (see Figure 3.2). Amla also contains flavonoids such as quercetin (Figure 3.2), kaempferol-3-O-α-L (6″ methyl) rhamnopyranoside and kaempferol-3-O-α-L (6″ ethyl) rhamnopyranoside [3].

3.2 TRADITIONAL AND VALIDATED USES

Amla is a very important medicinal plant in Ayurveda and in the various folk systems of medicine in Southeast Asia. Amla has been used for more than 3000 years in India and, according to Ayurvedic principles, its regular consumption is considered to be extremely useful in arresting degenerative and senescence processes, promoting longevity, enhancing digestion, reducing constipation, reducing fever, purifying blood, reducing cough, alleviating asthma, strengthening the heart, benefiting the eyes, stimulating hair growth, enlivening the body, and enhancing intellect [3].

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TABLE 3.1 Colloquial Name of Gooseberry in Different Languages [6,7]

Language	Names
Scientific name	*Phyllanthus emblica* L.; synonyms *Cicca emblica* Kurz; *Emblica officinalis* Gaertn. *Mirobalanus embilica* Burm. *Phyllanthus mairei* Lév.
Sanskrit	dhatriphala, amla, amaliki, amalakan, sriphalam, vayastha, amalaka, dhatri
Arabic	haliilaj, ihliilaj
Assamese	amlakhi, amlakhu, amlaku, amlaki
Bengali	amlaki, amla, dhatri, amloki
Chinese	an mole
English	Emblica myroblan, Indian gooseberry
French	Phyllanthe emblica
German	amla
Gujarati	amla, ambala, amala
Hindi	amla
Italian	Mirabolano emblico
Kannada	nellikkai, nellikayi, beta nelli, pottadenollikayi
Kashmiri	amli, embali
Khasi	sohmylleng
Konkani	aavalo, aavnlaa, awla, awla
Lao	mak kham bom
Malay	melaka
Malayalam	nellikka
Malaysian	popok melaka
Manipuri	heikru
Marathi	aavalaa, awla, avalkathi, aavalaa
Mizo	Sunhlu
Myanmar	zee phyu thee
Nepalese	amba, amala
Odiya	aanla
Portuguese	Mirabolano emblico
Punjabi	olay, ainla, anala, aula, amla
Sinhala	nelli
Tamil	nellikkai, nelli
Telugu	usiri, usirikaya, usiri
Thai	ma kham pom
Tibetan	skyu-ru-ra
Urdu	amla, amlaj

Amla is regarded as a crucial constituent of many polyherbal Ayurvedic preparations, such as *Amlakadi Gritha*, *Amlakadi Tailya*, *Amlakyadi Churna*, *Aamalaki Rasayanam*, *Asokarista*, *Avipatikara Churnam*, *Chyavananaprasa Leham*, *Dasamularishta*, *Dhatri Lauha*, *Dhatryarista*, *Kumaryasava*, *Panchatika guggulu Ghritam*, *Thriphala Lepam*, *Thriphala Guggulu*, *Thriphala Ghritam*, and *Thriphala Churnam* [3,4]. Amla is also used in Siddha, Unani, Thai, Tibetan, Sri Lankan, and Chinese systems of medicine [3]. Amla fruits are an important ingredient in the pharmaceutical industry and are used to prepare Ayurvedic/herbal healthcare products like hair oil, dye, shampoo, face creams, and tooth powder [3,4].

FIGURE 3.1 Photograph of amla fruits.

The fruits are indispensable in the various folk systems of medicine in Southeast Asia, and are used to treat ailments like diabetes, cough, asthma, bronchitis, cephalalgia, ophthalmopathy, erysipelas, skin diseases, hemorrhoids, nervous debility, leprosy, inflammation, emaciation, dyspepsia, colic, flatulence, hyperacidity, peptic ulcer, jaundice, strangury, diarrhea, dysentery, hemorrhage, leucorrhea, menorrhagia, cardiac disorders, intermittent fevers, anemia, jaundice, liver complaints, hematuria, osteoporosis, weak vision, and inflammation of the eyes [3,4].

Since antiquity amla has been shown to be beneficial in preventing and reducing age-related changes, and scientific studies carried out in accordance with the modern system of medicine have validated the ethnomedicinal claims. In the subsequent sections of this chapter the beneficial effects of amla in preventing diseases that increase with aging, such as cancer, diabetes, CVD, renal failure, immune suppression, arthritis, and cataract, are addressed in detail [2–7].

3.2.1 Amla in Diabetes

The global burden of diabetes is on the rise. It is estimated that 552 million people will be affected by 2030, of which 101.2 million are contributed by India. The highest incidence is seen among the age group 40–59 years [8]. Aging has been known to affect pancreatic β cell

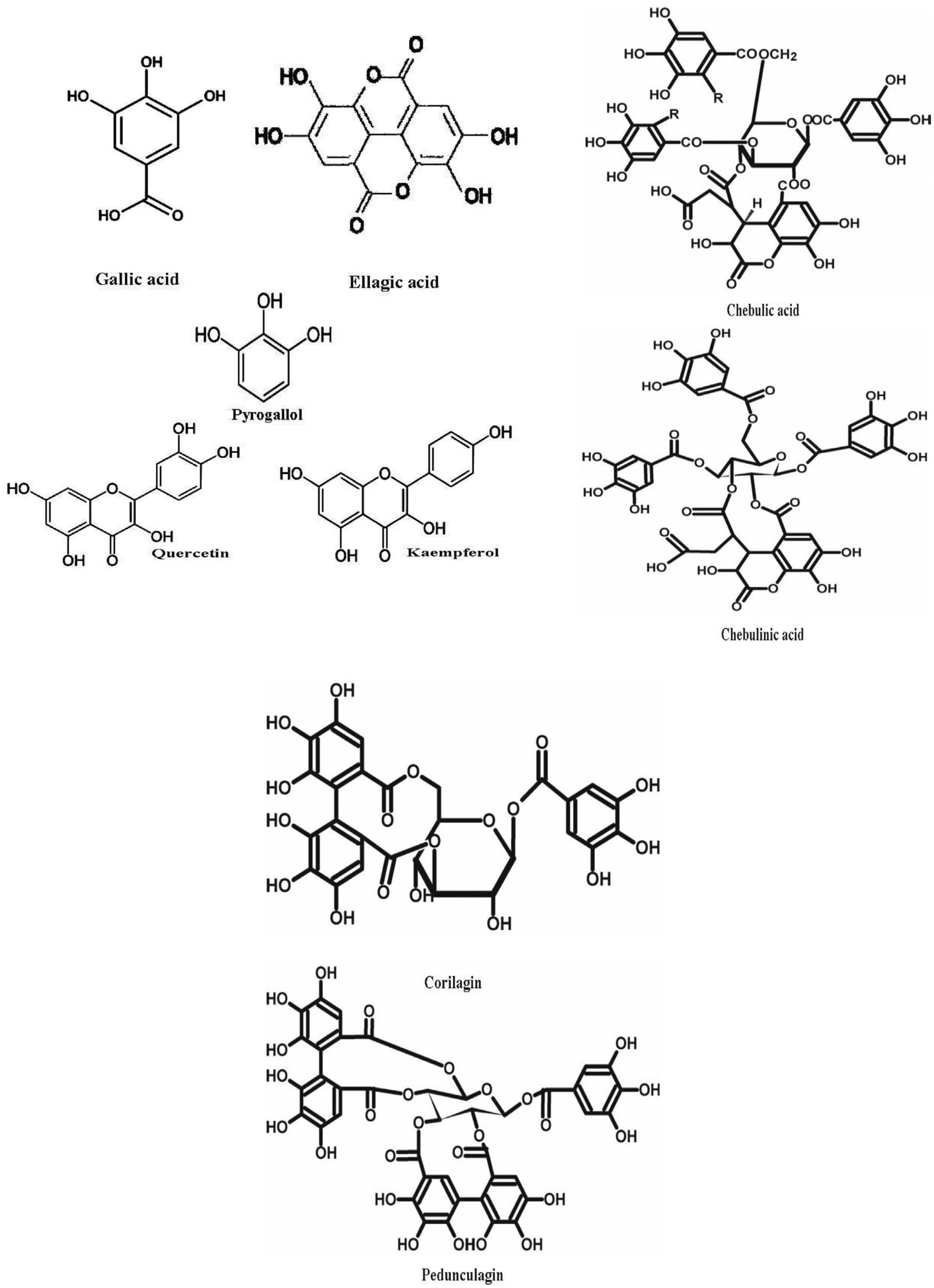

FIGURE 3.2 Some important phytochemicals of amla.

function, insulin secretion, and insulin sensitivity, thus playing a major role in the development of diabetes [9]. The gene associated with aging (*SIRT1*) has been linked with the development of diabetes, especially type 1 diabetes mellitus [10]. Oxidative stress is the key factor in the development of diabetes-related complications, and several plant polyphenols have been shown to be beneficial in diabetes. Amla (*Emblica officinalis*) contains tannins, alkaloids, vitamin C, gallic acid, and ellagic acid, which have antioxidant and immunomodulatory properties.

Several studies have demonstrated the ameliorative effects of amla in alloxan-, streptozotocin-, and high-fat diet-induced diabetic rats [11–14]. Oral administration of aqueous extract of amla (350 mg/kg) over a duration of 84 days decreased the levels of serum glucose, glycated hemoglobin, and glucose-6-phosphatase enzyme activity, while concomitantly increasing serum insulin and the glycogen stores in liver and skeletal muscle, and upregulating glucokinase in alloxan-induced type 1 diabetic rats [13]. After administering the ethanolic extract of amla (200 mg/kg) for 45 days a significant reduction in diabetes-induced atherogenesis and cardiac complications was seen among the streptozotocin-induced diabetic rats, thus endorsing its antihyperglycemic and antihyperlipidemic effects [3]. Amla extracts have also demonstrated significant free-radical scavenging activity, thus alleviating oxidative stress indices in the serum of diabetic rats. The levels of advanced glycosylation end products (AGEs) and thiobarbituric acid-reactive substances (TBARS), which have been shown to play a causative role in diabetes, decrease with amla ingestion [12].

3.2.2 Amla in Cardiovascular Disease

Globally, cardiovascular diseases (CVD) are the leading cause of death, accounting for more than 17 million deaths and contributing to approximately 30% of all deaths [15,16]. According to the most recent World Health Organization (WHO) data, more than 80% of all CVD deaths occurred in developing (low- and middle-income) countries, and estimates are that it will continue to dominate mortality trends worldwide in the future. Scientific studies by Mastan and colleagues [17] have shown that the aqueous extract of amla possesses cardiotonic activity. To further substantiate these observations, cell culture studies with cardiac myoblast H9c2 cells have also demonstrated that the ethanolic extract of amla was effective in ameliorating the doxorubicin-induced cytotoxicity secondary to its antioxidant properties [18]. Isoproterenol, a widely used experimental drug possessing β-agonistic properties, is used to produce myocardial stress and necrosis, thus inducing myocardial infarction. Oral administration of amla (100, 250, and 500 mg/kg) for 30 days was effective in preventing the isoproterenol-induced cardiotoxicity in rats. Amla increased antioxidants (SOD, CAT, GPx, and GSH), and decreased myocyte injury-specific marker enzymes (CPK-MB and LDH) and levels of LPx [19]. Among the phytochemicals, quercetin (10 mg/kg) given for 14 consecutive days was found to reduce the mitochondrial lipid peroxides and simultaneously to increase the mitochondrial antioxidants and the activity of isocitrate, succinate, malate, and α-ketoglutarate and NADH dehydrogenases and cytochrome-c-oxidase, thus ameliorating the isoproterenol-induced myocardial infarction in rats [20].

3.2.3 Amla in Renal Failure

The prevalence of chronic kidney disease (CKD) is increasing worldwide, with an annual growth rate of 8%. CKD is strongly associated with diabetes, hypertension, and chronic glomerulonephritis [21]. The loss of renal function as age progresses is a well-recognized phenomenon. A progressive fall in the glomerular filtration rate (GFR) and renal blood flow (RBF) has been documented. Eventually, a loss of renal mass, afferent arteriolar hyalinization, glomerular sclerosis, and tubulointerstitial fibrosis may occur as age advances. These changes make an aged kidney susceptible to developing acute kidney injury or chronic kidney disease [22]. The ethyl acetate extract of amla was found to reduce the levels of blood urea nitrogen and serum creatinine in aged rats. A significant reduction in the serum levels of thiobarbituric acid-reactive substances (TBARS), renal homogenate, and mitochondria in aged rats suggests that amla ameliorates oxidative stress during the aging process. Inducible nitric oxide synthase (iNOS) and cyclo-oxygenase (COX)-2 expression in the aorta of aged rats were also ameliorated by inhibition of NF-κB activation [23]. Patients with diabetic nephropathy on regular hemodialysis are found to have high levels of oxidative stress (due to neutrophil activation induced by hemoincompatibility between the hemodialyzer and blood). Though plain amla supplementation for 4 months in uremic patients led to a reduction in the plasma oxidative markers, it had no effect on diabetic and atherogenesis indices [24]. However, a mixture of green tea extract (epigallocathechin-3-gallate) and amla extract in a 1:1 ratio, given for 3 months, was found to improve significantly the diabetic and atherogenesis indices in uremic patients. Antioxidant defense was also found to improve substantially in those patients [25].

3.2.4 Amla in Cancer

The incidence of cancer increases with age. Among people above the age of 65 years, there is an 11-fold increase in the incidence of developing cancer as compared to younger individuals. The median age of cancer patients at death ranges from 71 to 77 years [26]. The radiomodulatory, chemomodulatory, and chemopreventive effects, free radical scavenging, and antioxidant, anti-inflammatory, antimutagenic, and immunomodulatory properties of amla have been demonstrated to be effective in the treatment and prevention of cancer. The phytochemicals of amla have been extensively studied in tert-butyl hydroperoxide (t-BH)-induced toxicity, as has their mechanism of hepatoprotective action in human hepatocarcinoma cells (HepG2 cell line). The hepatoprotective potential has been attributed to amla's ability to reduce lipid peroxidation and thus cellular damage [27]. Activator protein-1 (AP-1) and human papilloma virus (HPV) transcription are implicated in the pathogenesis for tumorigenicity of cervical cancer cells. Amla fruit extract was found to inhibit AP-1 by downregulating the constituent Ap-1 proteins c-Jun, JunB, JunD, and c-Fos. Viral transcription was simultaneously suppressed, resulting in inhibition of cervical cancer cells [28]. Amla extracts have also been shown to be effective in inhibiting the cell growth of lung, liver, cervical, breast, ovarian, and colorectal cancer cell lines by producing apoptosis, thus postulating its use as a chemotherapeutic agent in future [29].

3.2.5 Amla as an Immunomodulator

Amla, being a rich source of vitamin C, improves natural killer cell activity and antibody-dependent cellular cytotoxicity. The lifespan of tumor-bearing mice was found to increase by 35% [30]. Chromium has been used as an immunosuppressive agent in various research studies. The antioxidant and immunomodulatory effects of amla helped to suppress the enhanced apoptosis and DNA fragmentation caused by chromium [31]. Similar studies in chromium-fed mice found amla offered cytoprotection against oxidative injury in macrophages. The immunosuppressive effects of chromium against lymphocyte proliferation and IL-2 and IFN-γ production were also restored by amla [32]. Arsenic-induced oxidative stress and apoptosis observed in thymocytes of arsenic-fed mice were prevented by co-administration of amla, thus emphasizing the fact that amla has immunomodulatory properties [33]. *Emblica officinalis* extract was also studied as a radioprotective agent. Radiation of Swiss albino mice resulted in reduction of glutathione and catalase concentration in the intestines. Lipid peroxidation was also observed in the jejuna cells. These changes were absent when mice were treated with amla extract prior to irradiation [34].

3.2.6 Amla in Arthritis

Rheumatoid arthritis and osteoporosis are well-known to be associated with aging. Osteoclasts (OCs), the primary cells involved in bone resorption, are involved in the pathogenesis of most age-related bone disorders. Human rheumatoid synovial lymphocytes and fibroblasts promote osteoclastogenic activity by activating the receptor activator of the NF-κB ligand (RANKL). Tumor necrosis factor (TNF-α) and IL-7 are involved in the differentiation of osteoclasts, thus representing a link between inflammation and structural damage in joints [35]. Amla extracts were demonstrated to induce apoptosis of mature human primary OCs, by inducing the expression of Fas levels – part of the apoptotic pathway. Up to 50 μg/ml of amla extracts did not demonstrate any significant cytotoxic effects on the cell populations [36]. Ganju and co-workers [37] assessed the immunomodulatory properties of amla extracts in the adjuvant-induced arthritic (AIA) rat model. The lymphocyte proliferation activity and histopathological features of synovial hyperplasia were used to evaluate the anti-inflammatory response. A marked reduction in inflammation and edema in those treated with amla extracts proved its immunomodulatory properties, and thus its use as an effective therapeutic agent in the treatment of arthritis [37].

3.2.7 Amla in Cataracts

Visual blurring and cataracts are associated with aging. A 25-fold increase in the incidence of blindness is seen as a complication of diabetes. Advanced glycosylation end products, and activation of glucosamine pathways and polyol pathways, contribute to the pathogenesis of cataracts [38]. Aldose reductase has been implicated as a major therapeutic target in diabetic complications, especially cataracts. An important component of amla, β-glucogallin has been proven to selectively inhibit sorbitol accumulation by 73% in *ex vivo* organ culture models of lenses. Therefore, amla may be used as an aldose reductase inhibitor in the prevention of diabetic cataracts [39]. The aqueous extract of amla and its tannoids was found to be effective in delaying the onset of diabetic cataracts in streptozotocin (STZ)-treated rats. Though the oral administration of amla did not prevent STZ-induced hyperglycemia, cataract progression was significantly delayed when assessed with slit-lamp microscopy. It is thus hypothesized that amla counters polyol pathway-induced oxidative stress, preventing the aggregation and insolubilization of lens proteins [40]. In animal studies, especially those performed in frogs, amla extracts hastened the process of cell proliferation and dedifferentiation of the epithelial cells of the iris, thus inducing lens regeneration [41]. This study again corroborates the use of amla as a medicinal agent for preventing and delaying the development of cataracts.

3.2.8 Amla in Dermatological Diseases

Skin aging is a multifactorial process. Hyaluronic acid, which retains moisture, is the key molecule involved in sustaining the turgor and resilience of skin [42]. Aged skin, characterized by wrinkles, is secondary to decreased collagen content. Collagen synthesis is inhibited by the pro-inflammatory cytokine (TNF-α), and collagen degradation is enhanced by increased production of matrix metalloproteinase (MMP-9) [43]. Vitamins, carotenoids, tocopherols, flavonoids, and a variety of plant extracts possessing antioxidant properties have been widely used to maintain healthy skin. Ayurvedic cosmeceuticals dating back to the Indus Valley Civilization have utilized many traditional plant extracts, especially amla, for defying aged skin [44]. On mouse fibroblast cells, amla extracts at concentrations of 0.1 mg/ml were found to significantly promote type-1 pro-collagen levels, while simultaneously suppressing collagenase activity in a dose-dependent manner [45]. *Emblica* extracts have also been reported to possess a special property of promoting pro-collagen content while inhibiting the MMP, thus effectively inhibiting ultraviolet B (UVB)-induced photoaging in human skin fibroblasts [46]. *Emblica* has been proven to protect the skin from the damaging effects of free radicals, non-radicals, and transition metal-induced oxidative stress, and may be used as an effective sunscreen and anti-aging skin product [47].

3.2.9 Amla and Memory

Oxidative stress and reactive oxygen species (ROS) play a significant role in the brain signaling pathways. Mitochondria-generated ROS are implicated in cellular aging and, thus, cognitive impairment. A similar mechanism is implicated in the pathogenesis of Parkinson's disease [48]. *Emblica officinalis* has been traditionally used for CNS disorders in Ayurvedic medicine. Two groups of rats with kainic acid (KA)-induced seizures and cognitive deficits were studied, the first group being pretreated with hydroalcoholic extract of amla (700 mg/kg intraperitoneally).The group that received amla showed a significant suppression in cognitive decline and seizures, documented by way of decreased levels of TBARS and TNF-α, and increased levels of GSH [49]. Anwala churna, an Ayurvedic preparation of amla, was studied in different dosages in rats with diazepam-, scopolamine-, and aging-induced amnesia. A dose-dependent improvement in memory deficits was documented with amla extracts [50]. A potential therapeutic role of amla in Alzheimer's disease and other memory disorders may thus be elucidated.

3.3 CONCLUSION

Amla has been one of the most common medicinal components used in Alternative Medicine, especially Ayurveda, Unani, Siddha, and Chinese systems. The multiple and diverse medicinal effects of amla make it an inexpensive yet effective therapeutic agent devoid of adverse effects. Amla has been documented to prevent programmed cell death by reducing TBARS and suppressing iNOS and COX-2 expression in various cell lines, thus reducing the oxidative stress. The elevated expression of pro-apoptotic proteins (bax) was also significantly reduced with the oral administration of amla. The primary cause of intrinsic biologic aging is oxidative damage to macromolecules produced during the oxidative metabolism occurring in the mitochondria. Amla has been found to reduce age-related hyperlipidemia by attenuating the oxidative stress involved in lipid metabolism and protein expression during the aging process [6]. The tannoid principles emblicanin A, emblicanin B, punigluconin, and pedunculagin of amla have also been found to normalize stress-induced perturbations in oxidative free-radical scavenging activity, hence inhibiting the aging process [7]. Several diseases that have an increased incidence with aging have also responded to the therapeutic effects of *Emblica*, thus substantiating its role as an impressive and potent agent to prevent and delay aging.

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