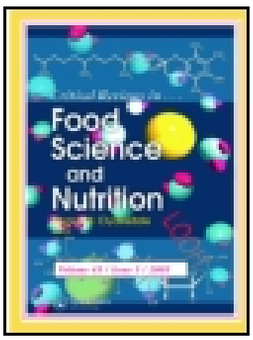

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New phytochemicals as potential human anti-aging compounds: Reality, promise, and challenges

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Abstract

Aging is an inevitable process influenced by genetic, lifestyle and environmental factors. Indirect evidence shows that several phytochemicals can have anti-aging capabilities, although direct evidence in this field is still limited. This report aims to provide a critical review on aspects related to the use of novel phytochemicals as anti-aging agents, to discuss the obstacles found when performing most anti-aging study protocols in humans, and to analyze future perspectives. In addition to the extensively studied resveratrol, epicatechin, quercetin and curcumin, new phytochemicals have been reported to act as anti-aging agents, such as the amino acid L-theanine isolated from green tea, and the lignans arctigenin and matairesinol isolated from *Arctium lappa*

seeds. Furthermore, this review discusses the application of several new extracts rich in phytochemicals with potential use in anti aging therapies. Finally, this review also discusses the most important biomarkers to test anti-aging interventions, the necessity of conducting epidemiological studies and the need of clinical trials with adequate study protocols for humans.

Key words: underexplored phytochemicals, anti-aging interveners, anti-aging study protocols, aging biomarkers, bioavailability

1. Introduction

Aging is a complex biological process characterized by a gradual loss of physiological integrity, leading to the decline of almost all physiological functions and increased vulnerability to death (López-Otin, Blasco, Partridge, Serrano & Kroemer, 2013; Lenart & Krejci, 2016). This progressive impairment constitutes the primary risk factor for important human pathologies, such as cancer, diabetes, cardiovascular disorders, as well as neurodegenerative diseases (Corella & Ordovásc, 2014).

It has been proposed that humans age in ‘‘spare parts’’ (in French: en pièces detachées), a process characterized by increasing losses of vital functions, some occurring faster, as the elastic functions, and others relatively slowly, as the nervous conductivity (Labat-Robert & Robert, 2014). The rapid decline in elastic functions such as accommodation, vascular and pulmonary elasticity, and, the most visible one, skin elasticity, involves major physiological functions. On the other hand, some aging mechanisms are not consequences of loss of function, but simply the repercussion of ‘‘illegal’’ chemistry in the body, for which no built in defenses exist, as it is the case of the non-enzymatic glycosylation (glycation) (Robert & Fulop, 2014).

Despite a century of research, no universally accepted theory regarding the molecular basis of aging has been postulated (Lenart & Krejci, 2016). In the past years, the aging research has experienced a groundbreaking advance, especially with the discovery that the rate of aging is controlled, at least partially, by genetic pathways and biochemical processes conserved in evolution. Hence, a central goal in aging research is to establish the molecular mechanisms that contribute to it. On the other hand, it is also known that the age-related processes determined by

genetics can be strongly influenced by the environmental factors (Stephan, Franke & Ehrenhofer-Murray, 2013).

In the past 30 years, the number of scientific articles regarding anti-aging interventions along with potential anti-aging compounds has exponentially increased, with an increment of more than 5-fold in the total of scientific research/review articles in the last 10 years (**Figure 1**). The present report aims to provide a critical review on aspects related to the use of phytochemicals as anti-aging agents, to discuss the obstacles found when performing most anti-aging study protocols in humans, and to analyze future perspectives. Investigations regarding the theme have immensely accelerated during the last ten years, what originated some recent review articles on anti-aging strategies involving natural dietary supplements (Rizvi & Jha, 2011), the anti-ageing activities of natural compounds (Argyropoulou, Aligiannis, Trougakos & Skaltsounis, 2013) and the possible mechanisms regarding the aging process (Manayi, Saeidnia, Gohani & Abdollahi, 2014), so that only publications after 2006 have been considered.

2. Anti-aging phytochemicals

Leonov et al. (2015) recently defined phytochemicals as structurally diverse secondary metabolites produced by plants and by non-pathogenic endophytic microorganisms living within plants. These compounds help plants to survive to environmental stresses and to protect them from microbial infections and environmental pollutants. Phytochemicals can also provide plants with a defense against herbivorous organisms and attract natural predators of such organisms in addition to lure pollinators and other symbiontes. Phytochemicals are present in a great variety of foods including fruits, vegetables, cereal grains, nuts and cocoa/chocolate likewise as in beverages such as juice, tea, coffee and wine (Si & Liu, 2014; Zhang et al., 2015).

Diet plays an essential role in daily human life, and dietary patterns and specific nutritional supplements may play a significant role in promoting human health and prolonging life. Current evidence suggests that eating a Mediterranean diet and supplementation with certain vitamins may decrease morbidity and mortality. Other strategies, such as caloric restriction (Sohal & Forster, 2014), rapamycin (Riera & Dillin, 2015) and resveratrol ingestion (Park & Pezzuto, 2015), have shown promising results in animal studies. However, despite some completed (Patel et al., 2011; Tomé-Carneiro et al., 2013; Ehninger, Neff & Xie, 2014) and ongoing clinical trials (available at the database http://clinicaltrials.gov/), data on the human responses are still incomplete (Adomaityte, Mullin & Dobs, 2014).

The knowledge that genetic mutations in diverse cellular pathways can boost lifespan has paved the idea that pharmacological inhibition of aging pathways could be the supreme tool to extend the lifespan and to slowdown the onset of age-related diseases. However, until the present, only a few compounds with such activities have been described and studied (Stephan, Franke & Ehrenhofer-Murray, 2013).

In addition to the extensively studied resveratrol, epicatechin, quercetin, curcumin, as well as the green tea extract and its epicatechins, other phytochemicals have been reported to act as anti-aging agents, inclusively in studies using animal models. **Table 1** and **Table 2** present compilations of some of these less known phytochemicals (extracts or isolated compounds, respectively) that have presented anti-aging potential both *in vitro* and *in vivo* in the past decade.

Jung et al. (2010) reported that myricetin (**Figure 2**), a phytochemical present in berries and red wine among several food matrices, inhibited wrinkle formation in mouse skin induced by chronic UVB irradiation. Myricetin treatment reduced UVB-induced epidermal thickening of

mouse skin and also suppressed UVB-induced matrix metalloproteinase-9 (MMP-9) protein expression and enzyme activity.

Kim et al. (2013) investigated whether caffeic acid, S-allyl cysteine, and uracil isolated from garlic (**Figure 3**) could modulate UVB-induced wrinkle formation and affect the expression of matrix metalloproteinase (MMP) and NF-κB signaling. They found that all three compounds significantly inhibited the degradation of type I procollagen and the expressions of MMPs *in vivo*. The compounds also attenuated the histological collagen fiber disorder and oxidative stress *in vivo* and decreased oxidative stress and inflammation by modulating the activities of NF-κB and AP-1.

In a very recent work, Ansel et al. (2016) investigated the anti-aging activity of *Fitchia nutans* Hook.f., an endemic plant previously used as a skin care ingredient included in a sacred traditional monoï preparation in French Polynesia. An extract of leaves of *F. nutans* was submitted to anti-aging activity assays using *ex vivo* human skin tests which revealed its potential in stimulating collagens and elastin dermal growth. The main constituents of the *F. nutans* extract were identified: sesquiterpenoids (including 15-isovaleroyloxydihydrocostunolide, a new natural compound shown in **Figure 2**), phenylpropanoids, and phenolic derivatives.

3. Anti-aging study protocols in humans

In the past years, eminent progress on the understanding of aging mechanisms has been achieved through the study of model organisms such as the yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster* and the mouse *Mus musculus* (Briga & Verhulst, 2015). However, there is a lack of human studies, including large-scale clinical trials.

Epidemiological studies have evidenced that diet plays a pivotal role in the pathogenesis of many age-associated chronic diseases as well as in the biology of aging itself (Pounis et al., 2013; Rizza, Veronese & Fontana, 2014). The Mediterranean diet, based on the consumption of olive oil and abundant in plant-derived foods like fruits, vegetables, legumes, nuts and whole grains, has since long been recognized as one of the most salutary dietary patterns (Freitas-Simoes, Rosa & Sala-Vila, 2016).

Resveratrol (RES), reasonably present in the Mediterranean diet, has been proposed as one of the most important dietary constituents involved in vasculoprotection. Epidemiological data have linked moderate intake of RES-containing red wine with a significant decrease in the risk of coronary artery disease (Labinskyy et al., 2006). Kasiotis, Pratsinis, Kletsas & Haroutounian (2013) summarized the available evidence indicating that RES and its related stilbenes possess both anti-aging and anti-angiogenic properties. As stated by the authors, on one hand RES maintains vascular fitness through its antioxidant, anti-inflammatory, anticoagulant and fat-lowering activities, while on the other hand it can inhibit angiogenesis, thus further potentiating its anti-tumoral effects. According to Tomé-Carneiro et al. (2013), evidence from experiments in humans has generally endorsed the cardioprotective activity of resveratrol through effects related to the improvement of inflammatory markers, atherogenic profile, glucose metabolism and endothelial function. These same authors, however, have commented on the incongruences between *in vitro* studies and the evidence obtained in studies conducted with humans with respect to the effects of resveratrol. Besides summarizing and discussing the (still scarce) evidence obtained from randomized clinical trials they also provided a critical outlook for further

research on this molecule that is evolving from a minor dietary compound to a possible multi-target therapeutic drug.

Khan & Mukhtar (2013) reviewed the major epidemiological and clinical studies on green tea (*Camelia sinensis* (L.) Kuntze) consumption and human cancer prevention in different organs, cancer being the current major cause of mortality throughout the world. The authors also presented evidence for the association between tea drinking and a dininished occurrence of diabetes, arthritis and disturbances in the neurological system (all age-related diseases) in humans. However, Khan & Mukhtar (2013) highlighted that results from human studies are not always positive, possibly, due to the fact that higher doses of tea are used in animal studies than those consumed by humans and that in animal studies the experimental conditions are generally optimized for the evaluation of a protective effect. Hence, they concluded that large scale and well controlled human clinical trials are still needed to determine with exactitude the health promoting effects of tea consumption. Even so, Khan & Mukhtar (2013) expressed the opinion that the current findings authorize to recommend the consumption of green tea to the aging population.

Epidemiological studies have shown an inverse relationship between nut intake and chronic diseases such as cardiovascular diseases and cancers. Yang (2009) have summarized various epidemiological, animal models and culture cell studies evidencing that Brazilian nuts may slow down the aging process, stimulate the immune system, and protect against heart disease and certain forms of cancer. According to the author Brazil nuts are abundant in dietary antioxidants, especially selenium (Se), an essential element with antioxidant, proapoptotic, anticancer and DNA repair properties (Shankar, Kumar & Srivastava, 2013). Brazil nuts also contain phenolic

acids and flavonoids in both free and bound forms and are abundant in tocopherol, phytosterols, and squalene (**Figure 4**). Phytochemical extracts from Brazil nuts exhibit antioxidant and antiproliferative activities, and the majority of the total antioxidant and antiproliferative activities arise from the combined action of phytochemicals and selenium (Yang, 2009).

Parkinson's disease (PD) is the second most common neurodegenerative disease, being directly related to aging. Several mechanisms have been implicated in the pathogenesis of PD including oxidative stress, mitochondrial dysfunction, protein aggregation, and inflammation. Evidence from animal models shows that various phytochemicals may alter the mechanisms contributing to PD pathophysiology. In addition, epidemiological studies have demonstrated a relationship between reduced risk of PD and diet. In this context, Sha & Duda (2015) have proposed that phytochemicals in plant-based foods may contribute to neuroprotection in PD and that adopting a plant-based diet may provide symptomatic improvement and alter the progression of the disease.

Very recently, Julián-Ortiz et al. (2016) summarized clinical evidences on the advantages of using phytochemicals as adjuvant therapy along with conventional anticancer therapies. Their findings showed that the beneficial effects of phytochemicals are virtue of their direct anti-carcinogenic activity, induction of relief in cancer complications, as well as to their protective role against the side effects of the conventional chemotherapeutic agents. According to the authors, curcumin, ginsenosides, lycopene, homoharringtonine, aviscumine, and resveratrol are amongst the phytochemicals with the most remarkable amount of clinical evidence indicating their direct anticancer activities in different types of cancer. However, Julián-Ortiz et al. (2016) highlighted the lack of evidence from clinical trials in the case of a large number of

phytochemicals and recommended further human studies to confirm the role of plant metabolites in the management of cancer.

3.1.Difficulties in performing anti-aging study protocols

Despite the increasing amount of *in vitro* studies trying to unravel the mechanisms of action of phytochemicals, the research in this field is still deficient and fragmented. There are many unanswered questions concerning particularly the transfer of the findings of the *in vitro* studies to the *in vivo* situation, to acertain the validity of the recommendation to consume phytochemicals-enriched food or phytochemical supplements, including anti-aging supplements. Furthermore, human epidemiological studies or clinical investigations are very few and non-systematic.

Some important aspects should be carefully considered in human study protocols. A first point of attention is that phytochemicals are present in food matrices together with many other components, and it is possible that their *in vivo* activity may be the result of a synergism with other factors (Rossi et al., 2008). Another important issue is the bioavailability of antioxidant phytochemicals, as any systemic potential activity attributed to a dietary compound involves its absorption and delivery to the target tissue in its intact form or as an active metabolite (Larrosa, García-Conesa, Espín & Tomás-Barberán, 2010). Most *in vitro* studies on the biological activity of polyphenolic compounds use the original molecule present in the plant, without taking into account that, *in vivo*, they are in fact transformed into derivatives. Hence, ideally, the *in vitro* studies should use the selected metabolites produced *in vivo* in order to accurately assess the authentic activity of phenolic compounds (Rossi et al., 2008).

3.2. *Erythrocytes and plasma: a viable model system to assess anti-aging effects of phytochemicals in humans*

It is well known that eukaryotic cells display a plasma membrane redox system (PMRS) that transfers electrons from intracellular substrates to extracellular electron acceptors. About a decade ago, Rizvi et al., (2006) conducted studies to determine the activity of PMRS in human erythrocytes as a function of age and to correlate this activity to the total plasma antioxidant capacity as an effort to understand the role of PMRS in human aging. The study was carried out on 80 normal healthy subjects of both genders between the ages of 18 and 85 years. The activity of erythrocyte PMRS was estimated by following the reduction of ferricyanide. The total antioxidant capacity of the plasma was estimated in terms of the ferric reducing ability of plasma (FRAP) values. The authors observed an age-dependent decrease in the total plasma antioxidant capacity measured in terms of FRAP values. A highly significant correlation was observed between PMRS activity and plasma FRAP values. Therefore, Rizvi, Jha & Maurya (2006) concluded that the increased PMRS in erythrocytes during aging correspond to a protective mechanism of the system for efficient extracellular DHA reduction and ascorbate recycling under the condition of increased oxidative stress.

After a few years, Pandey & Rizvi (2010) reviewed the aging process focusing on the importance of some reliable markers of oxidative stress, which could be applied as biomarkers of the aging process in human studies. In their review, the authors discussed that several parameters have being used to evaluate the extent of oxidative damage, but not all of them can be used as biomarkers of the aging process because many of them are influenced by several factors including sex, types of tissue, diet and also by their efficient repair mechanisms. Furthermore, some parameters are also dependent upon the methods used to measure them. Finally, the authors proposed the use of erythrocytes as model cells for the study of aging and age-related diseases,

arguing that erythrocytes provide an array of biochemical parameters which have been successfully applied to assess aging-related changes in the redox status.

3.3.Evaluation of antioxidant effects of phytochemicals in human cells

Overproduction of oxidants, reactive oxygen species (ROS) and reactive nitrogen species (RNS), in human body can cause an imbalance and lead to oxidative damage to large biomolecules such as lipids, DNA, and proteins. This damage is responsible for the pathogenesis of several human diseases, including aging (Zhang et al., 2015). The antioxidant defense system includes endogenous and exogenous antioxidants. The main endogenous (enzymatic and non-enzymatic) antioxidants are superoxide dismutase, catalase,glutathione peroxidase, and glutathione (Pham-Huy, He & Pham-Huy, 2008). ROS can also activate enzymes such as the metalloproteinase collagenase, the serine-protease elastase and the mucopolysaccharase hyaluronidase (all involved in degrading the extracellular matrix components), which results in visible skin aging. However, several *in vitro* scientific studies have shown that phytochemicals can reduce oxidant levels and thus inhibit collagenase, elastase, hyaluronidase and tyrosinase enzymes (Bravo, Alzate & Osorio, 2016).

Exogenous antioxidants include vitamins, carotenoids and polyphenols, with the diet being the main source. Martins, Barros & Ferreira (2016) recently published a reference work on the aspects related to the *in vivo* antioxidant activity of phenolic extracts and compounds from plant origin. In this critical review, the biological functions in the human metabolism were discussed, comparing *in vivo* versus *in vitro* studies, as also focusing the conditioning factors for phenolic compounds bioavailability and bio efficacy. Furthermore, the authors provided an upcoming perspective about the use of phytochemicals as life expectancy promoters and anti-aging factors

in human individuals. Antioxidants have the capacity to disarm ROS by functioning as reducing agents (Pham-Huy, He & Pham-Huy, 2008). This antioxidant activity capable of scavenging ROS is a property that may be primarily attributable to their phenolic hydroxyl groups, depending on their number and position as well as to their glycosylation patterns. Generally, thus, phytochemicals with more hydroxyl groups may have a stronger antioxidant capacity (Si & Liu, 2014). Endogenous and exogenous antioxidants act interactively (e.g., synergistically) to maintain or re-establish redox homeostasis (Bouayed & Bohn, 2010).

3.4. *Evaluation of skin aging and the influence of phytochemicals used in anti-aging formulations*

The impact of human aging is especially visible in the skin, where it originates several changes, including thinning, dryness, laxity, fragility, enlarged pores, fine lines and wrinkles (Wang, Chen, Huynh & Chang, 2015). Skin aging is also linked to physical disorders of the skin, being caused by both intrinsic and extrinsic factors (Farage, Miller, Elsner & Maibach, 2008), all leading to reduced structural integrity and loss of physiological function (Landau, 2007). Progerin, a truncated version of the lamin A protein, cooperates with telomeres to trigger cellular senescence in normal human fibroblasts. Progerin accumulates over time as the skin ages and, thus, its expression is greater in older fibroblasts than in younger ones (Wang, Chen, Huynh & Chang, 2015).

Tissue degeneration, inherently linked to aging, becomes more significant through the lack of tissue regeneration, which can be exemplified by the well-known loss of telomeric ends leading to cellular senescence (Kammeyer & Luiten, 2015). Kammeyer & Luiten (2015) believe that oxidative processes is the main cause of tissue deterioration or aging. For the authors, while

senescence is a *status quo* for individual cells, oxidative degeneration is a progressive event and affects the entire tissue composition. It will fatally triumph, unless there is inexhaustible availability of antioxidants and substantial tissue regeneration, which will retard the aging process.

A gerontogen can be defined as an environmental stimulus, exposure, or toxicant that accelerates the rate of molecular aging (Sorrentino, Sanoff & Sharpless, 2014). Incident toxicants such as arsenic and benzenes (Zhang, Lin, Funk & Hou, 2013), ionizing radiation and UV light (Freund, Patil & Campisi, 2011), cigarette smoke (Song et al., 2010), side effects of therapeutic treatments (cytotoxic chemotherapy and HIV therapy), psychological stress, as well as alterations in diet and exercise (Sorrentino, Sanoff & Sharpless, 2014, Kim et al., 2016), all correspond to gerontogen examples. Extrinsic aging is generated by injurious free radicals produced in response to various environmental factors, including sun exposure and smoking. These radicals induce damage to the skin by causing an inflammatory reaction.

According to Kammeyer & Luiten (2015), damaged protein and glycosaminoglycan structures that form the events for extracellular matrix degradation, such as that of collagen, are the pivotal structural components responsible for an aged skin appearance. As stated in their recent review, UV-induced damage of DNA can lead to mutations and consequential apoptosis or malignant transformations of cells, and UV-exposure can directly damage biomolecules, or indirectly via the generation of radicals. The injury to these structures generate cell death, degraded proteins and inflammatory responses. Moreover, reactive intermediates, often radicals, can further danificate other biomolecules. In addition, Kammeyer & Luiten (2015) stated that these findings are frequently clearer from experiments *in vitro* than *in vivo*, by virtue of the

tricky interpretation of the results obtained *in vivo* by the potential occurrence of adaptive responses (mitohormesis).

Rhodes et al. (2013) studied the effects of the supplementation of green tea catechin (GTC) metabolites in humans. The authors proved that GTC metabolites can be effectively incorporated into the human skin and reported its protective effects against cutaneous inflammation induced by UV radiation in association with reduced production of the pro-inflammatory eicosanoid 12-hydroxyeicosatetraenoic acid. However, Farrar et al. (2015) which performed a double-blind, randomized, placebo controlled trial to examine whether GTCs protect against clinical, histologic, and biochemical indicators of UVR-induced inflammation, did not found such positive effects. These authors reported that the oral administration of GTC did not significantly ameliorate skin erythema, leukocyte infiltration, or eicosanoid response to UVR inflammatory process.

In the past decade, consumers became more suspicious about chemical ingredients. Hence, there is a trend of going back to fundamental or basic cosmetic products with an increasing request for natural and environmentally sustainable products, such as, for example, pharmaceutical herbal formulations (Wang, Chen, Huynh & Chang, 2015).

Various anti-aging agents in cosmeceuticals are consumed orally, but these are also known to work topically in the elevation of skin health (Singh & Agarwal, 2009). Anti-aging herbal cosmetics may contain isolated bioactive compounds or crude phytoextracts. Currently, there are extensive research activities in progress involving development and characterization of extract loaded formulations to concurrently achieve various goals such as anti-inflammatory and anti-aging effects (Jeon, Kim, Kim & Lee, 2009).

Jadoon et al. (2015) presented an extensive list of *in vivo* antioxidant studies on herbal creams loaded with phytoextracts. The botanicals studied for dermatologic use in cream form comprised: *Acacia nilotica* (L.) Del., *Benincasa hispida* (Thunb.) Cogn., *Caltha officinalis (*L.) Moench., *Camellia sinensis, Nelumbo nucifera* Gaertn., *Capparis decidua* (Forssk.) Edgew., *Castanea sativa* Mill., *Coffea arabica* var. *angustifolia* Cramer, *Crocus sativus* L., *E. officinalis, Foeniculum vulgare* Mill., *Hippophae rhamnoides* L., *Lithospermum erythrorhizon* Siebold & Zucc., *Malus domestica* Borkh., *Matricaria chamomilla* L., *Moringa oleifera* Lam., *Morus alba* L., *Ocimum basilicum* Linn., *Oryza sativa* L., *Polygonum minus* Huds., *Punica granatum* L., *Tagetes erecta* Linn., *Terminalia chebula* Retz., *Trigonella foenumgraecum* L., and *Vitis vinifer*a. According to these authors, the observed anti-aging effect of cream formulations is probably an end result of a coordinated action of multiple components of the formula, being that, among several phytochemicals, the phenolic acids and flavonoids appear to be effective against UVR-induced damage. Jadoon et al. (2015), however, highlighted the importance of more evidence-based studies for their anti-aging effects.

Silymarin/silibinin, naturally occurring flavonolignans present in milk thistle (*Silybum marianum* (L.) Gaertn.) and artichoke (*Cynara cardunculus* (L.) subsp. *scolymus* Hayek) (**Figure 4**), can be found in some commercialized high-end moisturizers to prevent cutaneous oxidative damage and photoaging. Their anti-aging potential is embased by studies in the mouse skin model with silymarin/silibinin showing strong protective effects against environmental toxicants as well as UVB radiation (Singh & Agarwal, 2009).

Latest studies have evidenced a trend of using agro-industrial by-products as sources of phytochemicals for diverse applications, including anti-aging cosmetics. In a recent review

Rodrigues, Pimentel & Oliveira (2015) proposed the application of olive by-products, a proven source of antioxidant compounds like oleuropein (shown in **Figure 4**). These by-products also present interesting fatty acids and mineral profiles. Likewise, Chulasiri (2016) suggested the use of pigmented rice bran, rich in phytochemicals including gamma-oryzanol, tocopherols, tocotrienols and phenolic compounds, as a matrix for obtaining safe and efficient anti-aging cosmeceuticals.

Apparently, the synergy of combining the topical use of anti-aging creams with oral food supplements seems to be an interesting approach for preventing and slowing down skin aging (Rodrigues, Pimentel & Oliveira, 2015).

4. The hallmarks of aging and potential anti-aging interventions using phytochemicals

In a landmark paper, López-Otin, Blasco, Partridge, Serrano & Kroemer (2013) have summarized the principal theories of aging, namely (1) genomic instability, (2) telomere attrition, (3) epigenetic alterations, (4) loss of proteostasis, (5) deregulated nutrient sensing, (6) mitochondrial dysfunction, (7) cellular senescence, (8) stem cell exhaustion, and (9) altered intercellular communication. These nine hallmarks of aging were classified by the authors into three categories: primary hallmarks, antagonistic hallmarks, and integrative hallmarks. According to the authors, primary hallmarks would be those decisively negative, what is the case of DNA damage, including chromosomal aneuploidies, mitochondrial DNA mutations and telomere loss, epigenetic drift, and defective proteostasis. Contrarily, the antagonistic hallmarks would be those hallmarks that present opposite effects depending on their intensity: at low levels, they mediate beneficial effects, though at high levels, they become deleterious. Senescence is included in this category, since it protects the organism from cancer but, in excess, can promote

aging. Likewise ROS mediating cell signaling as well as optimal nutrient sensing and anabolism, which are all clearly important for survival but, in excess and with time, can promote negative effects like aging itself. The third category contains the integrative hallmarks (stem cell exhaustion and altered intercellular communication), which directly influence tissue homeostasis and function.

Critical questioning related with the large disparity of lifespan between mice and humans, has been published recently (Margolick & Ferrucci, 2015). In fact, it cannot be simply assumed that mechanisms of aging found in mice will pertain equally to aging in humans. However, it is possible to find many similarities in phenotypes of aging across humans and other mammalian species, and definition of a standard phenotype of aging would allow the underlying mechanisms to be tested experimentally.

Table 3 presents how the phytochemicals could potentially be applied as possible interveners against aging markers, and the studies conducted both *in vivo* and *in vitro* that support this proposal. These phytochemicals were formerly known as antioxidants and are now being revisited due to their capabilities to change the epigenome (Christodoulou et al., 2014). In **Table 3**, efforts were done to correlate the terms phytochemicals, hallmarks of aging and potential anti-aging interventions

5. Conclusion, limitation and future perspectives

The potential function of phytochemicals as human anti-aging compounds has been well endorsed by the studies described herein, suggesting their possible role either in preventing age-related diseases and in “slowing down” aging itself, even slightly. The impact of human aging on its more obvious manifestation, the skin aging, has also been herein contemplated. Besides

providing a broad compilation of both phytochemical extracts and isolated compounds from still underexplored plant/food sources, this article presents a critical review on phytochemicals as plausible interveners against the major hallmarks of aging, inclusively due to their epigenetic properties **(Table 3).** More importantly, this work proposes a discussion about the challenges and limitations in performing human study protocols, and evidences the scarcity of well-designed epidemiological studies and clinical trials addressing the anti-aging effects of phytochemicals.

Considering not only the eminent research interest in validating phytochemicals as authentic interveners for delaying aging and associated conditions, but also the ultimate ambition of geroscience to discover strategies to boost natural defenses and prolong healthspan through better management of the threats posed to an individual's cells and tissues, some future directions could be proposed:

1. The precise identification of specific molecules involved in the anti-aging activities of phytochemical extracts and phytochemical supplements is of major importance, in order to determine which is the genuine anti-aging component responsible for the attributed effects, without neglecting the synergistic interactions among the various compounds.

2. Several related variables should be adequately investigated in human trials, namely the bioavailability and bio-efficacy of the anti-aging phytochemicals as well as drug-phytochemical interactions.

3. There is a clear need to devise novel accessible, predictive and relevant biomarkers to test anti-aging interventions. Hence, the possibility of using the markers erythrocytes and plasma as a model system to assess anti-aging effects of phytochemicals in humans should be better explored.

4. Still on the issues involving human anti-aging study protocols, further investigations should consider whether a potential anti-aging phytochemical would be applicable to everyone, as it is already known that individuals age differently (Riera & Dillin, 2015).

5. Further large scale and well controlled human clinical trials are needed to determine the actual effects of both well-known and underexplored anti-aging phytochemicals. Only based on these findings, recommendations of consumption by the human population should be made.

Lastly, despite the past decade advances, our knowledge regarding the potential of phytochemicals as anti-aging agents is still restricted. Hopefully in future, with the required well conducted epidemiological studies and clinical trials adopting adequate study protocols for humans, along with the promising novel epigenetics and nutrigenomics tools, and also taking into account the heterogeneity of aging, science can unravel the true significance of the phytochemicals as agents of human anti-aging compounds.

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Table 1. Phytochemical extracts with proven anti-aging effects reported in the last decade, some still underexplored by science or little known, listed by alphabetic order of plant matrix.

Plant Matrix	**Extracts**	***In vitro* assays or animal model**	**Novelty, main contribution**	**Ref.**
Aconitum carmichaelii Debeaux	Aqueous extract	Cell culture and Rats	*A. carmichaelii* has presented protective effects on SH-SY5Y cells apoptosis induced by 1-methyl-4-phenylpyridinium. In addition, *A. carmichaelii* regulated the expression of genes related to the metabolism of sex hormones, facilitating thus the conversion of sex hormones, and reducing their inactivation.	Qiu et al. (2012), Wang et al. (2012)
Alchornea triplinervia (Spreng.) Müll.Arg.,	Methanolic extracts	Enzymatic assay	Among all extracts, fractions and sub-fractions tested, *G. erecta* and *U. myricoides* fruits showed the most	Bravo, Alzate and Osorio

Gaultheria erecta (Vent.) Kuntze, *Rubus compactu*s Utsch and *Ugni myricoides* (Kunth) O.Berg, among thirty-five Andean plants at different stages of growth			interesting results for inhibitory activity against skin aging-related enzymes and antioxidant properties.	(2016)
Citrus sunki Hort. ex Tanaka (Jingyul), *Citrus unshiu* Marcov, *Citrus sinensis* Osbeck, *Citrus reticulata* Blanco	Citrus-Based Juice Mixture (CBJM)	Cell culture and Mice	The CBJM not only inhibited both H_2O_2-induced cell damage and intracellular ROS production in human dermal fibroblasts, but also increased the expression levels of antioxidant enzymes (namely glutathione reductase, catalase and manganese superoxide dismutase).	Kim et al. (2016)

(Hallabong) and *Vitis vinifera* L. (white grape)			Furthermore, the oral administration of CBJM clearly diminished skin thickness and wrinkle formation while elevating collagen level in an ultraviolet light B-exposed hairless mouse model.	
Cuscuta chinensis Lam.	Ethanolic extract	Rats	*C. chinensis* showed a potential anti-aging effect in animals, as it significantly inhibited the non-enzymatic glycosylation reaction of aging mice after induction by D-galactose.	Li, Deng, Li and Li (2013)
Elaeis guineensis Jacq.	Methanolic leaf extract	Antioxidant assays	The assessed extract showed promising antioxidant capacity, with an IC_{50} value of 814 μg/mL in the DPPH assay, 534.04 μg/mL for the nitric oxide-scavenging activity assay, 37.48 μg/mL	Soundararajan and Sreenivasan (2012)

			for the xanthine oxidase inhibition assay and 1052.02 µg/mL for the hydrogen peroxide scavenging activity assay. Besides, it presented a high concentration of total phenolics (0.33 mg / g of dry extract).	
Emblica officinalis Gaertn (Indian fruit)	Ethanolic extract	Cell culture	The *E. officinalis* (EO) extract, at concentrations ranging from 10-40 µg/mL, was able to inhibit cellular proliferation and to protect pro-collagen 1 against UVB-induced depletion by inhibition of UVB-induced MMP-1. In addition, treatment with EO extract also prevented the UVB disturbed cell cycle, thus decreasing UVB-induced photoaging in human skin fibroblasts by virtue of its	Adil et al. (2010)

			strong ROS scavenging ability.	
Euterpe oleracea Mart. (Açai palm fruit)	Fruit pulp	*Drosophila melanogaster*	Açai supplementation (2%) clearly improved the lifespan of female flies fed a high fat diet compared to a non-supplemented control. Açai raised the transcript levels of both l(2)efl (a small heat-shock-related protein) and two detoxification genes, GstD1 and MtnA, at the same time it diminished the transcript level of phosphoenolpyruvate carboxykinase, a pivotal gene involved in gluconeogenesis.	Sun et al. (2010)
Fitchia nutans Hook.f. (Polinesian cosmeticeutical	Cyclohexane/ether (2:1) extract	Cell culture and *ex vivo* human skin tests	The *F. nutans* leaves extract was assessed for its anti-aging effects using *ex vivo* human skin tests, what evidenced its efficacy on stimulating	Ansel et al. (2016)

ingredient)			collagens and elastin dermal growth. The main constituents of the plant extract were identified: sesquiterpenoids (among which 15-isovaleroyloxy-dihydrocostunolide, a novel natural compound), phenylpropanoids and phenolic derivatives (**Figure 2**).	
Hedysarum austrosibiricum B.Fedtsch. and *Hedysarum polybotrys* Hand.-Mazz.	Aqueous extract and isolated polysaccharide	Aged Rats and Aging Mice	The tested *H. austrosibiricum* extracts diminished the malondialdehyde content of both liver and brain tissues of D-galactose-induced aging rats. These extracts increased the activities of SOD and glutathion peroxidase, while decreased the activity of monoamine oxidase activity in the brain tissue. Thus *H. austrosibiricum* presented	Dong et al. (2013)

			anti-aging effects both by eliminating free radicals and activating antioxidases. Likewise, a polysaccharide isolated from *H. polybotrys* have significantly improved SOD contents in the erythrocytes of aged rats, what also suggests an anti-aging effect via activation of antioxidases.	
Helichrysum niveum Graham	Methanolic extracts and isolated acylphlorog lucinol derivatives	Enzymatic assay	Promising total antioxidant capacities, with low values of IC_{50} obtained from oxygen radical absorbance capacity, ferric-ion reducing antioxidant power, trolox equivalent absorbance capacity and inhibition of Fe^{2+}-induced lipid peroxidation assays, were found for helinivenes 1 and 2. These two compounds also	Popoola, Marnewic, Rautenbach, Iwuoha and Hussein (2015)

			presented anti-tyrosinase activities.	
Labisia pumila (Blume) Mez (Malasian popular herb)	Aqueous extract	Cell culture	Treatment with *L. pumila* extract (LPE) clearly decreased both the pro-inflammatory cytokines production and the expression of cyclooxygenase. After LPE treatment the collagen, synthesis in human fibroblasts, negatively affected by UVB, was restored to normal levels.	Choi et al. (2010)
Picea mariana (Mill.) Britton, Sterns & Poggenb, *Pinus banksania* Lamb., *Abies balsamea* (L.) Mill, *Betula alleghaniensis*	Hot water and ethanolic extracts	Enzymatic assay	Extracts from six Canadian forest species were assessed for their phenolic compounds contents, and their capacity to inhibit lipid peroxidation and to scavenge reactive species (nitric oxide and singlet oxygen) involved in inflammatory diseases and	Royer, Prado, García-Pérez, Diouf and Stevanovic (2013)

Britton, *Populus tremuloides* Michx. and *Acer rubrum* L.			skin aging. The extracts were also tested over their capacities to inhibit tyrosinase and elastase. The results showed that all polyphenolic bark extracts, but especially those from *A. rubrum*, *P. banksania*, *B. alleghaniensis* and *P. mariana*, present anti-aging potential.	
Portulaca oleracea L. (Asian herb)	Ethanolic extracts	Cell culture	The bioactivities of *P. oleracea* ethanolic extracts of were assessed under various conditions with NIH3T3, B16F10, and MCF-7 cell line model systems. The tested extracts promoted inhibition of tyrosinase, however were not effective in suppressing either the TYRP-1 or DCT expression in B16F10 cells. In addition, *P. oleracea*	Rui et al. (2009)

			extracts presented anti-inflammatory effects on TNF-α-stimulated NIH3T3/NFκB-Luc cells and raised the synthesis of collagen on NIH3T3 cells.	
Sonchus oleraceus (L.) L	Methanolic extract of the leafs	Cell culture	*S. oleraceus* extracts (at 5 mg/mL or above) significantly supressed H_2O_2 stress-induced premature senescence, and the herein anti-aging effect was concentration-dependent. When compared to the corresponding ascorbic acid treatments, *S. oleraceus* extracts showed better or equivalent effects.	Ou, Rades and McDowell (2015)
Vaccinium angustifolium Aiton	Total phenolic compounds extract and	*Caenorhabditis elegans*	The complex mixture of blueberry phenolic compounds increased lifespan and slowed down aging	Wilson et al. (2006)

(Blueberry)	a proantho-cyanidin (PAC)-enriched fraction		related declines in *C. elegans*. Although blueberry treatment increased survival during acute heat stress, it did not protected against acute oxidative stress.	

Table 2. Isolated phytochemicals with proven anti-aging effects reported in the last decade, some still underexplored by science or little known.

Compound category	**Food/Plant Source**	**Isolated compounds**	***In vitro* assays or animal model**	**Novelty, main contribution**	**Ref.**
Flavonoids	*Epimedium koreanum* Nakai	Flavonoids	Rat	With the progression of aging, the mean levels of phosphorylation of p65, IκBα and IκBε in rat spleen lymphocytes decreases. However, the intragastric administration of *E. koreanum* flavonoids strongly up regulated the expression of Rel/NF-κB family and increased the phosphorylation of p65, IκBα and IκBε during aging.	Liu et al. (2008)
Flavonols	Red wine, Onions, Green	Quercetin (purified compoun	Cell culture	The authors have identified quercetin and its derivative quercetin caprylate as proteasome activators with	Chondrogianni et al. (2010)

	tea, Apples and Berries	d)		antioxidant properties capable of alter the cellular lifespan, survival and viability of HFL-1 primary human fibroblasts. A rejuvenating effect was inferred when these compounds were supplemented to already senescent fibroblasts.	
Flavonols	Berries and Red wine	Myricetin (purified compound) (**Figure 2**)	Mice	Myricetin treatment diminished UVB-induced epidermal thickening of mouse skin and suppressed UVB-induced matrix metalloproteinase-9 protein expression, as well as enzyme activity. Myricetin apparently exerted its anti-aging effects via suppression of UVB-induced Raf kinase activity and subsequent attenuation of UVB-induced phosphorylation of of	Jung et al. (2010)

				mitogen-activated protein kinase kinase1 (MEK) and the extracellular signal-regulated kinase (ERK) in mouse skin.	
Flavones	*Passiflora caerulea* L. (Blue passion flower), *Oroxylum indicum* (L.) Kurz (Indian trumpet flower) and Mushrooms	Chrysin (purified compound)	Mice	Chrysin significantly diminished the reactive species levels and attenuated the inhibition of superoxide dismutase, catalase and glutathione peroxidase, as well as the activity of Na^+ and K^+-ATPase, of aged mice of aged mice.	Souza et al. (2015b)

Stilbenoids	*Blueberries and Grapes*	Pterostilbene (purified compound)	Mice	The promising anticarcinogenic potential observed in this experiment was attributed to pterostilbene's role in maintaining the skin antioxidant defenses (glutathione levels, catalase, superoxide, and glutathione peroxidase activities) close to control values, as well as its capacity to inhibit UVB-induced oxidative damage.	Sirerol et al. (2015)
Lignans	*Arctium lappa* L.	Six lignans isolated from *A. lappa* seeds: arctigenin, matairesinol,	*Caenorhabditis elegans*	All tested lignans significantly extended the mean lifespan of *C. elegans*, inclusively under oxidative stress conditions. However, the strongest effect was observed with matairesinol, which at a concentration of 100 μM extended the life span of worms by 25%. A	Su and Wink (2015)

		arctiin, (iso) lappaol A, lappaol C, and lappaol F (**Figure 3**)		hypothetical underlying mechanism of the herein longevity-promoting activity of *A. lappa* lignans involves the DAF-16 mediated signaling pathway.	
Terpenes	*Pinus densiflora* Siebold & Zucc., *Pinus sylvestris* L. and *Abies grandis* (Douglas ex D.Don) Lindl.	Dehydro abietic acid (DAA)	*Caenorhabditis elegans*	The authors suggestes DAA as an anti-aging reagent, since it not only presented lifespan extension effects in *C. elegans*, but also prevented lipofuscin accumulation, and also prevented collagen secretion in human dermal fibroblasts. As stated by the authors, the herein anti-aging effects of DAA are primarily mediated by SIRT1 activation.	Kim et al. (2015)

Xantonoids	*Anemarrhena asphodeloides* Bunge	Mangiferin	Cell culture and Mice	*In vitro* results showed that mangiferin inhibited both UVB-induced gelatinase B expression and enzyme activity, thus attenuating the UVB-induced phosphorylation of MEK and ERK. In the *in vivo* studies, mangiferin diminished UVB-induced mean length and mean depth of skin wrinkle.	Kim et al. (2012)
Hydroxycinnamic acid, aminoacid and nitrogenous base	*Allium sativum* L. (garlic)	Caffeic acid, S-allyl cysteine and uracil (**Figure 3**)	Mice	The three compounds significantly inhibited both the degradation of type I procollagen and the expression of matrix metalloproteinases *in vivo*, at the same time that ameliorated the histological collagen fiber disorder and oxidative stress *in vivo*, and decreased oxidative stress and inflammation via the	Kim et al. (2013)

				modulation of NF-κB and AP-1 activities.	
Amino acids	Tree nuts and peanuts	L-Arginine (purified agmatine)	Rats	L-Arginine (40 mg/ kg) supplemented intraperitoneally notably enhanced spatial working memory and object recognition memory in aged rats, eliminated age-related elevation in total nitric oxide synthase (NOS) activity, and repaired endothelial NOS protein to the normal level. However, L-arginine supplementation did not improve exploratory activity and spatial reference learning and memory in aged rats.	Rushaidhi, Collie, Zhangb and Liu (2012)
Amino acids	*Camellia sinensis* (L.) Kuntze	L-Theanine (**Figure**	*Caenorhabditis elegans*	L-theanine improved survival of *C. elegans* in the presence of paraquat at a concentration of 1 μM, while extended *C.*	Zarse, Jabin and Ristow

	(green tea)	**2**)		*elegans* lifespan when applied at concentrations of 100 nM. Considering these findings, L-theanine may be worth testing in mammals and potentially humans concerning anti-aging effects.	(2012)
Proteins	*Daucus carota* L. (carrot)	Carrot glycoprotein	Cell culture	Carrot glycoprotein neutralizes reactive oxygen species, protect cell membrane, and plays a role as anti-aging agent in the exposed solar ultraviolet light skin	Lee, Jeong and Jang (2015)
Polysaccharides	*Lycium barbarum* L. (Chinese red-colored fruits)	Polysaccharides	Aged mice	*Lycium babarum* polysaccharides and vitamin C were administrated to aged mice. The therapeutic antioxidant effects were confirmed by attenuation of lipid peroxidation, improvement in antioxidant	Li, Ma and Liu (2007)

				enzymes and stimulation of immune systems	

Table 3. The hallmarks of aging and potential anti-aging interventions using phytochemicals.

Hallmarks of aging	**Possible anti-aging interventions**	**Role of phytochemicals - outstanding reviews or original contributions**	**Ref.**
Cellular senescence	Clearance of senescent cells	*Sonchus oleraceus* extracts protected cells against H_2O_2-induced senescence by mediating oxidative stress.	Ou, Rades and McDowell (2015)

		Delaying senescence or even promoting death of accumulating apoptosis-resistant senescent cells are current strategies to prevent age related diseases. Quercetin provenly display senolytic effects in some primary senescent cells, likely because of its inhibitory effects on specific anti-apoptotic genes (PI3K and other	Malavolta et al. (2016)

		kinases). The recent review *Pleiotropic Effects of Tocotrienols and Quercetin on Cellular Senescence: Introducing the Perspective of Senolytic Effects of Phytochemicals* discussed the role of quercetin as adjuvant in the therapy of cancer and preventive anti-aging strategies.	

Mitocondrial dysfunction	Mitohormetics, mitophagy	*Ginkgo biloba* L. extract (GBE) apparently possess direct protective effects on mitochondria. In an experiment with two age groups (3-week-old and 40-week-old) of a senescence-accelerated strain of mice, the responses of GBE on mitochondrial function in platelets and hippocampi were tested. The investigated	Shi et al. (2010)

		mitochondrial functions, assessed as cytochrome c oxidase activity, mitochondrial adenosine-5'-triphosphate content and mitochondrial glutathione content, diminished with age. GBE inhibited mitochondrial dysfunction in platelets of both young and old mice, evidencing a peripheral effect of *Ginkgo biloba* in	

		preventing and treating age-associated degeneration.	

Desregulated nutrient sensing	Dietary restriction (DR), IIS and m-TOR inhibition, AMPK and sirtuin activation	Seven sirtuins (SIRT) have been identified in mammals. One of them, SIRT-1 apparently mediate the beneficial effects on health and longevity of both caloric restriction and resveratrol.	Markus and Morris (2008)

		A review entitled *Resveratrol, sirtuins, and the promise of a DR mimetic*, explores the role of resveratrol as a mimic agent of DR. As such, resveratrol extends the lifespan of yeast, worms, flies, and of the short-living species of a fish. In rodents, resveratrol improves health, and prevents the early mortality	Baur et al. (2006); Baur (2010)

		associated with obesity, however its precise mechanism of action remains controversial, and extension of normal lifespan has not been found.	

Epigenetic alterations	Epigenetic drugs	Bioactive phytochemicals, which are abundantly available with minor toxic effects, have been assessed for their role in epigenetic modulatory activities in gene regulation for both cancer prevention and therapy. Favourably, several bioactive phytochemicals potentially interfered in expression of key tumor	Shukla et al. (2014)

		suppressor genes, tumor promoter genes and oncogenes via modulation of DNA methylation and chromatin modification in cancer. These investigated phytochemicals, either alone or in combination with other bioactive phytochemicals, presented encouraging results against various cancers.	

Stem cell exaustion	Stem-cell-based therapies	N-acetyl-l-cysteine (NAC) is an altered form of the amino acid cysteine that in turn occurs in foods derived from plant sources like bananas, onion, garlic and peppers.	Cerny and Guntz-Dubini (2013)

		NAC, a precursor of glutathione and a direct ROS scavenger, apparently restores aged stem cell function by targeting toxic metabolites. NAC treatment clearly restored the quiescence and reconstitution capacity of ATM-null HSCs24, while also improved survival of a distinct population of myogenic stem	Oh, Lee and Wagers (2014)

		cells in skeletal muscle, both *in vitro* and *in vivo*. However, it remains unclear whether NAC or other antioxidant treatments have a direct or indirect effect on age-dependent deficits in stem cells or stem cell function, and to elucidate these issues further investigations are required.	

Altered intercellular communication	Anti-inflammatory phytochemicals	*Ilex paraguariensis* A.St.-Hil. (yerba mate) ethanolic extracts showed a clear anti-inflammatory potential in culture cell tests, as well as outstanding antioxidant and interesting anti-tumor properties.	Souza et al. (2015a)

		Likewise, hydro-methanolic extracts of three different cultivars of globe amaranth (*Gomphrena haageana* Klotzsch, *Gomphrena globosa* var. *albiflora* Moq. and *Gomphrena* sp., respectively red, white and pink), all rich in quercetin-3-O-rutinoside, presented expressive anti-inflammatory potential and valuable	Liberal et al. (2016)

		properties related to oxidative stress.	

Loss of proteostasis	Activation of chaperones and proteolytic systems	Neurohormetic phytochemicals such as resveratrol, sulforaphanes and curcumin might protect neurons against injury and disease through increasing the production of antioxidant enzymes, neurotrophic factors, protein chaperones and other proteins that enhance the cell tolerance against stress.	Mattson and Cheng (2006)

		The oxidoreductase chaperone disulfide isomerase (DI), responsible for catalysing the maturation of disulfide-bond-containing proteins, is involved in the pathogenesis of both Parkinson's and Alzheimer's diseases. S-Nitrosylation of DI cysteines, cause by nitrosative stress, is linked to cytosolic debris	Pal, Cristan, Schnittker and Narayan (2010)

		accumulation and Lewy-body aggregates in both diseases. It was suggested that the phytochemicals curcumin and masoprocol could prevent DI from becoming S-nitrosylated and maintain its catalytic function under conditions mimicking nitrosative stress by forming stable NOx adducts.	

Genomic instability	Elimination of damaged cells	Pre-treatment with cinnamic acid provides effective radioprotection of human lymphocytes against the deleterious effects of irradiation with X-rays.	Cinkilic et al. (2014)

		A recent review entitled *Dietary phytochemicals and cancer prevention: Nrf2 signaling, epigenetics, and cell death mechanisms in blocking cancer initiation and progression* explores the potential of phytochemicals in inhibiting the evolution of carcinogenesis by activating both the apoptotic pathway and cell cycle arrest.	Lee et al. (2013)

Tellomere attrition	Telomerase reactivation	Due to the incomplete replication of linear chromosomes by DNA polymerase, telomeric repeats at the ends are lost which each cell division. Dysfunction of telomers is associated with the development of many age-related diseases. Telomere length and attrition of telomeric repeats can be altered by	Paul (2011)

		nutrition not only in human but also animal models, as it is well-established that many minerals, vitamins and phytochemicals such as polyphenols of green tea and grape as well as curcumin, can be helpul in DNA repair and chromosome maintenance.	

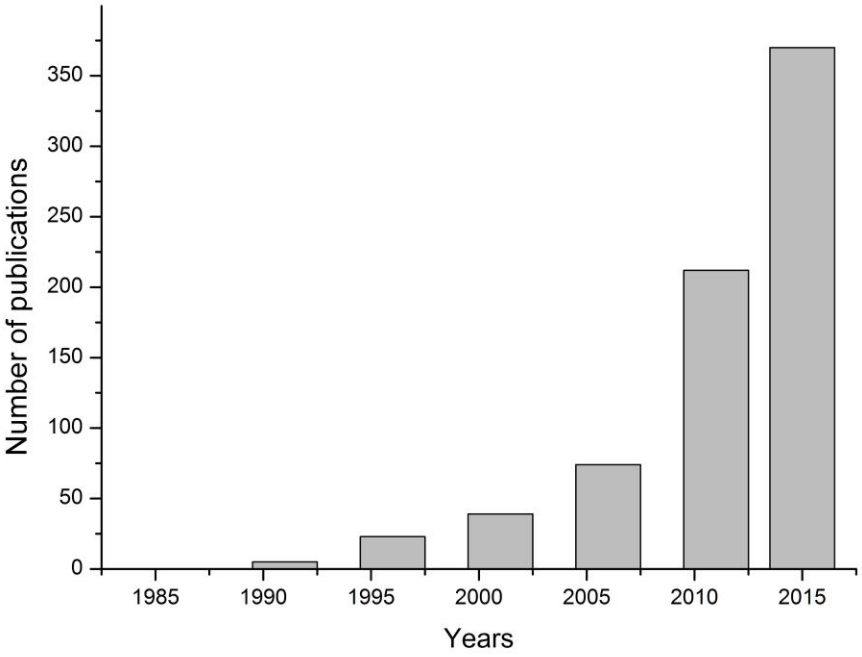
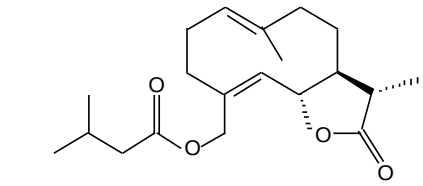
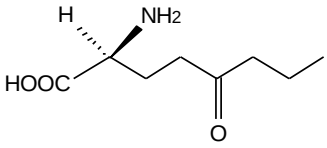


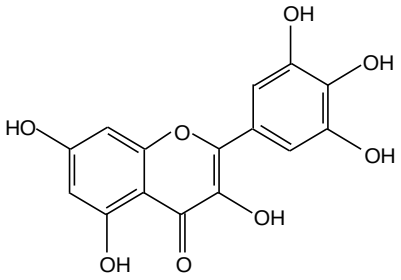
Fig. 1. Number of research articles and reviews published in the period from 1985 to 2015 regarding both "anti-aging" and "anti-ageing" terms, at the search domain of Science & Technology (obtained from Web of Science, May 2016; keywords restricted to the topics: anti-aging and anti-ageing).



8:15-Isovaleroyloxydihydrocostunolide



Theanine



Myricetin

Fig. 2. Chemical structures of the novel natural compound 8:15-isovaleroyloxydihydrocostunolide, a sesquiterpenoid recently identified in the extract of *Fitchia nutans;* the amino acid L-theanine, found in *Camellia sinensis* (green tea) among other sources; and the flavonol Myricetin, abundantly present in berries and red wine.

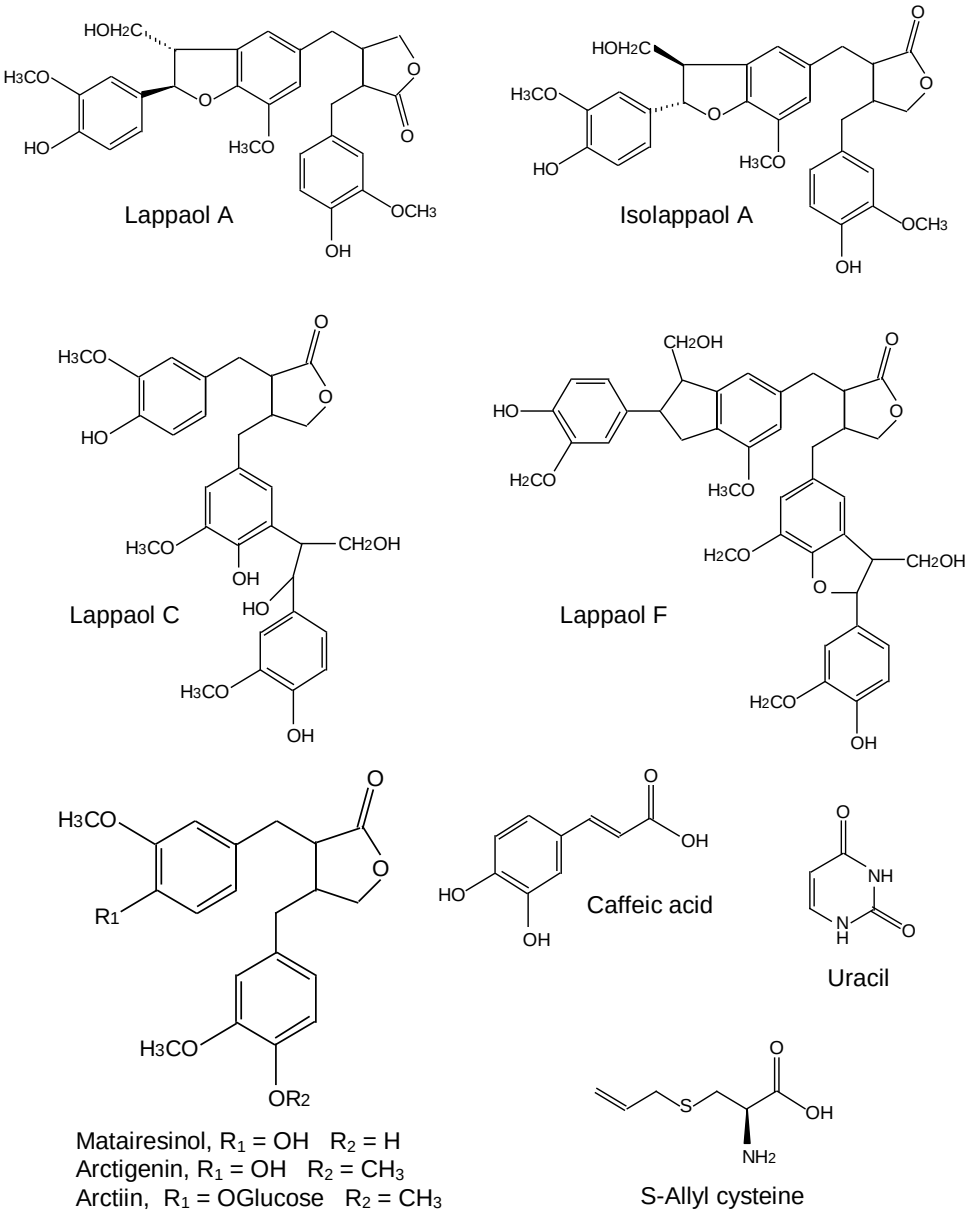


Fig. 3. Chemical structures of six lignans isolated from *Arctium lappa* seeds, namely arctigenin, matairesinol, arctiin, (iso) lappaol A, lappaol C, and lappaol F. Additionally, three compounds isolated from *Allium sativum* (garlic): caffeic acid, uracil and S-allyl cystein.

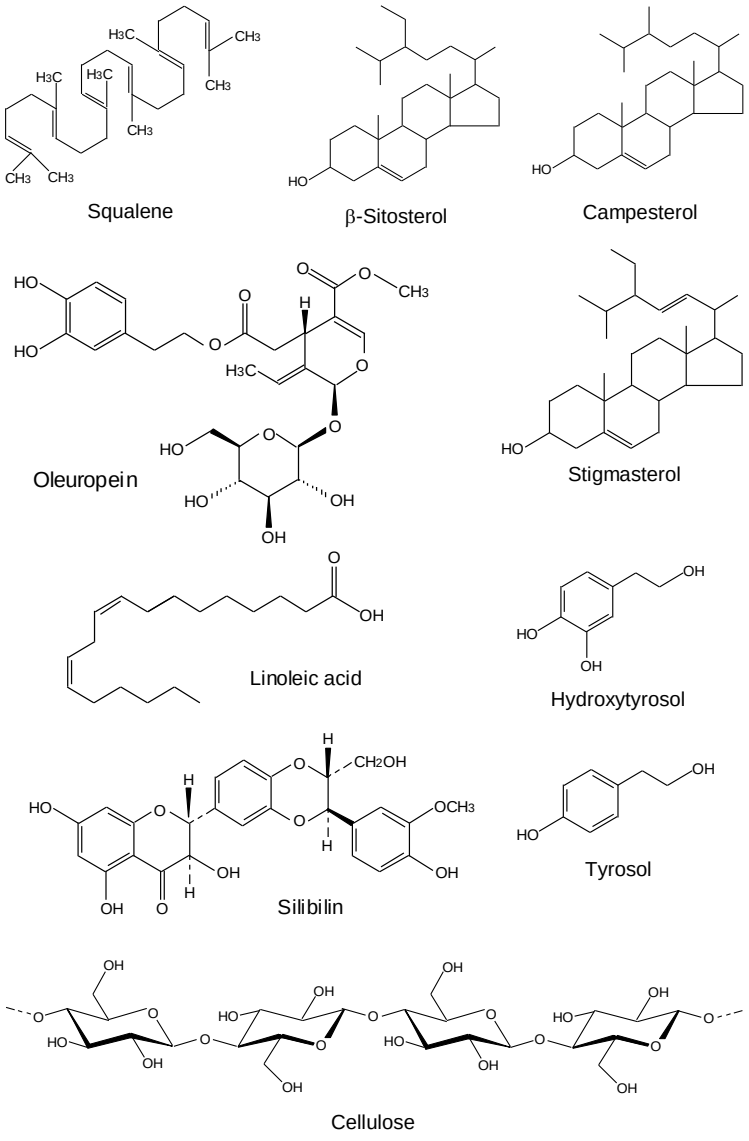


Fig. 4. Chemical structures of phytochemicals identified in Brazilian nuts (*Bertholletia excelsa*), namely the hydrocarbon steroid precursor squalene, and the phytosterols β-sitosterol, campesterol, and stigmasterol; structures of different compounds with skin effects identified in olive by-products, including oleuropein; and also silibinin, a flavonolignan abundantly present in milk thistle (*Silybum marianum*) and artichoke (*Cynara scolymus*).