



Check for updates

REVIEW

REVISED Exploring the anti-aging potential of natural products and plant extracts in budding yeast *Saccharomyces cerevisiae*:

A review

[version 2; peer review: 2 approved, 3 approved with reservations]

Phaniendra Alugoju^{1,2}, Chella Perumal Palanisamy^{id}³,
Naga Venkata Anusha Anthikapalli⁴, Selvaraj Jayaraman⁵,
Anchalee Prasanskulab^{id}⁶, Siriporn Chuchawankul^{id}⁷, Madhu Dyavaiah⁸,
Tewin Tencomnao^{id}^{1,2}

¹Department of Clinical Chemistry, Faculty of Allied Health Sciences, Chulalongkorn University, Bangkok, 10330, Thailand

²Natural Products for Neuroprotection and Anti-Ageing Research Unit, Chulalongkorn University, Bangkok, 10330, Thailand

³Department of Chemical Technology, Faculty of Science, Chulalongkorn University, Bangkok, 10330, Thailand

⁴Department of Chemistry, A.N.R College, Gudivada, Andhra Pradesh, 521301, India

⁵Centre of Molecular Medicine and Diagnostics (COMManD), Department of Biochemistry, Saveetha Dental College & Hospital, Saveetha Institute of Medical & Technical Sciences, Saveetha University, Chennai, Tamilnadu, 600077, India

⁶College of Public Health Sciences, Chulalongkorn University, Bangkok, 10330, Thailand

⁷Department of Transfusion Medicine and Clinical Microbiology, Faculty of Allied Health Sciences, Chulalongkorn University, Bangkok, 10330, Thailand

⁸Department of Biochemistry and Molecular Biology, Pondicherry University (A Central University), Puducherry, 605 014, India

V2 First published: 04 Oct 2023, 12:1265
<https://doi.org/10.12688/f1000research.141669.1>

Latest published: 17 Dec 2024, 12:1265
<https://doi.org/10.12688/f1000research.141669.2>

Abstract

Historically, plant derived natural products and their crude extracts have been used to treat a wide range of ailments across the world. Biogerontology research aims to explore the molecular basis of aging and discover new anti-aging therapeutic compounds or formulations to combat the detrimental effects of aging and promote a healthy life span. The budding yeast *Saccharomyces cerevisiae* has been, and continues to be, an indispensable model organism in the field of biomedical research for discovering the molecular basis of aging. *S. cerevisiae* has preserved nutritional signaling pathways (such as the target of rapamycin (TOR)-Sch9 and the Ras-AC-PKA (cAMP-dependent protein kinase) pathways, and shows two distinct aging paradigms: chronological life span (CLS) and replicative life span (RLS). This review explores the anti-aging properties of natural products, predominantly derived from plants, and phytoextracts using *S. cerevisiae* as a model organism.

Open Peer Review

Approval Status

	1	2	3	4	5
version 2					
(revision)					
17 Dec 2024			view	view	view
version 1					
04 Oct 2023	view	view			


1. **Srinivasa Rao Sirasanagandla** ^{id}, Sultan Qaboos University, Muscat, Oman
2. **John Hartman** ^{id}, University of Alabama-Birmingham, Birmingham, USA
3. **Marco Eigenfeld** ^{id}, Medical University Graz, Graz, Australia


Keywords

Saccharomyces cerevisiae, Replicative lifespan (RLS), Chronological lifespan (CLS), nutrient signalling pathways, target of rapamycin (TOR), Protein kinase A (PKA), Adenylate cyclase (AC)



This article is included in the **Cellular Senescence in Stress and Aging** collection.

4. **Hemagirri Manisekaran** , Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia, Pulau Pinang, Malaysia

5. **Weiwei Dang** , Baylor College of Medicine, Houston, USA

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding authors: Madhu Dyavaiah (madhud14@yahoo.co.in), Tewin Tencomnao (tewin.t@chula.ac.th)

Author roles: **Alugoju P:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Palanisamy CP:** Formal Analysis, Investigation, Writing – Original Draft Preparation, Writing – Review & Editing; **Anthikapalli NVA:** Data Curation, Formal Analysis, Investigation, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Jayaraman S:** Formal Analysis, Investigation, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Prasanskulab A:** Writing – Review & Editing; **Chuchawankul S:** Writing – Review & Editing; **Dyavaiah M:** Conceptualization, Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Tencomnao T:** Funding Acquisition, Project Administration, Resources, Software, Supervision, Visualization

Competing interests: No competing interests were disclosed.

Grant information: This research was funded by Chulalongkorn University (ReinUni_65_03_37_12).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2024 Alugoju P *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Alugoju P, Palanisamy CP, Anthikapalli NVA *et al.* **Exploring the anti-aging potential of natural products and plant extracts in budding yeast *Saccharomyces cerevisiae*: A review [version 2; peer review: 2 approved, 3 approved with reservations]** F1000Research 2024, 12:1265 <https://doi.org/10.12688/f1000research.141669.2>

First published: 04 Oct 2023, 12:1265 <https://doi.org/10.12688/f1000research.141669.1>

REVISED Amendments from Version 1

- As suggested by both reviewers, we have revised the abstract by include a statement of the objective and focus of the research (in version 2), removing philosophical and physiological descriptions of aging present in version 1.
- Reviewer 2 suggested removing the utility of model organisms and basic aspects of aging in version 1 to focus on natural products and plant extracts in the revised manuscript (version 2).
- We have highlighted the advantages and disadvantages of using yeast model in the version 2, which were not mentioned in version 1.
- A separate section compiling both emerging trends and future developments in the anti-aging research is included in version 2, which was not present in version 1.
- As suggested by reviewer 2, separate sections on CLS and RLS paradigms were included with additional citations in version 2, whereas they were compiled under same heading in version 1.
- Figure 2 has been expanded regarding to detail the genes and pathways in version 2, by removing the picturesque constraints of the cell and organelles represented as a yeast cell in version 1.
- The section entitled “conserved nutrient-sensing aging regulatory pathways,” which was under-cited in version 1, has been revised with sufficient citations in version 2.
- A list of natural products with anti-aging activities is provided in version 1. As suggested by reviewer 2, natural products have been reorganized under separate sub-headings in version 2.
- As suggested by reviewer 2, separate tables summarizing the natural products and plant extracts including their anti-aging mechanisms, have been included in version 2, which were not present in version 1.
- We have briefly mentioned in version 2 how different factors such as carbon sources, amino acid composition, pH of the growth medium affects CLS, which was not included in version 1.

Any further responses from the reviewers can be found at the end of the article

Introduction

Aging is an inevitable natural phenomenon characterized by gradual decline in the bodily functions with an increased susceptibility to various internal and external environmental cues and subsequent development of a plethora of chronic diseases, ultimately ending up with death. Aging is considered a major risk factor for the development of several disease conditions including diabetes, cancer, cardiovascular diseases, and neurodegenerative diseases.^{1–3} Several hallmarks of aging have been proposed including mitochondrial dysfunction, cell senescence, genome instability, telomere abrasion, epigenetic alterations, malfunction of autophagy, aberrant nutrient-sensing signalling, stem cell dysfunction/exhaustion, and loss of intercellular communication.^{4,5} Globally, there is an increase in the aging population and concomitant increase in the chronic diseases affecting the quality of life of elderly.^{6,7} Currently existing anti-aging strategies, such as dietary or caloric restriction (CR), exercise, and exogenous bioactive supplements, have shown to be promising in delaying or preventing chronic diseases and promoting active longevity in humans.^{8,9} However, life style associated anti-aging strategies like CR, exercise, and improved sleep quality alone may not be sufficient to delay aging and prevent age-related comorbidities, highlighting the need for the development of additional strategies, such as dietary supplements based on natural products from medicinal plants.⁹

Since ancient times, humans have been exploring natural products, including plants, not only for their food needs but also for the treatment of various ailments. Historically, medicinal plants have been used in various therapeutic formulations in the form crude extracts, decoctions, and gels. Plants have formed the basis of diverse traditional medicinal systems, including Indian Ayurveda, Chinese, Egyptian, and Unani medicine. The oldest records dating back to around 2600 BCE, document the use of about 1000 plant derived substances, such as oils, for the treatment of various ailments like cough, colds, infections, and inflammations in Mesopotamia. These oils were extracted from plant species including *Cedrus*, *Cupressus sempervirens*, *Glycyrrhiza glabra*, and others. Around 1500 BCE, it was documented in Papyrus Ebers that more than 700 plants derived drugs were used in Egyptian medicine.¹⁰ By 1100 BCE, the Chinese Materia Medica recorded about 1,215 plant-based drugs.¹¹ Likewise, Sushruta and Samhita have documented 857 herbal drugs in Ayurveda.¹²

According to the World Health Organization (WHO), about 65% of the global population depends on the traditional plant-based medicine for primary healthcare needs. It has been reported that approximately 80% of the pure compounds

that are used as drugs were derived from only 94 plant species.¹³ Moreover, a variety of derivatives of pure compounds are developed as drugs for treating different human diseases. For instance, an alkaloid compound, galegine, isolated from *Galega officinalis* formed the basis for the synthesis of anti-diabetic drugs such as metformin and other biguanide derivatives.¹⁴ Likewise, papaverine, isolated from *Papaver somniferum*, formed the basis for the synthesis of drugs like verapamil for treating hypertension, and pain relief drugs morphine and codeine.^{14,15}

It is no surprise that traditional plant-based medicine has always played a critical role in discovering and developing several drugs to cure human diseases. For example, in the early 1600s, the bark of *Cinchona* species was used to treat fevers in Amazon and Europe. In 1820, the antimalarial alkaloid compound quinine was isolated from the bark of *Cinchona officinalis*,¹⁵ forming the basis for the synthesis of other anti-malarial drugs such as chloroquine and mefloquine. Likewise, *Artemisia annua* has been widely used to treat fevers in Traditional Chinese Medicine. In 1972, an antimalarial drug artemisinin was isolated from *A. annua*.¹⁶ Other clinically important drugs developed from medicinal plants include, the anti-hypertensive drug reserpine from *Rauwolfia serpentina*, the anti-asthmatic drug ephedrine from *Ephedra sinica*, anticancer drugs such as vinblastine and vincristine from *Catharanthus roseus* and, and paclitaxel from *Taxus baccata*.^{17–19} Despite the extensive scientific exploration of terrestrial plants, only 6% of about 300, 000 plant species have been systematically examined, pharmacologically, and only 15% were investigated phytochemically.²⁰

Several natural product-based products have also been approved by the United States Food and Drug Administration (FDA). For example, Veregen™, a topical ointment for genital warts consisting of a mixture of green tea catechins, was approved in 2006.²¹ Sativex®, a neuropathic pain-relieving formulation composed of cannabis plant derived dronabinol 1 and cannabidiol 2, was approved in 2005.²² It was also approved in 2007 for use as an analgesic for cancer patients.²³ Qutenza®, a transdermal patch containing capsaicin, an active component of hot chili peppers, was approved in 2009 and has also been used against neuropathic pain.²⁴ This point to the fact that natural products or their derivatives has always been attracted a great attention owing to their ability to serve as templates for the invention and development of therapeutically active formulations or drugs against multiple chronic illness.

Previous studies have demonstrated the longevity promoting activity of several chemical compounds (known as geroprotectors) to ameliorate hallmarks of aging and to promote healthy lifespan of a variety of model organisms. However, only a very few compounds have been investigated for their potential geroprotective activity in the older people.²⁵ The main objective of the biogerontology research is to explore the molecular basis of aging and age-related diseases and to discover new interventions to counteract the detrimental effects of aging and related pathological conditions.^{26,27} The budding yeast *Saccharomyces cerevisiae* is one of the widely used model organisms not only for the understanding of aging and age-related diseases, but also as a potential tool for the discovery and evaluation of a wide spectrum of the pharmacological properties including anti-aging potential of several natural products and plant extracts.^{28–30} In this review, we have summarized the anti-aging effects of natural products, mostly plant derived and plant extracts in the budding yeast *S. cerevisiae*.

The budding yeast *Saccharomyces cerevisiae* – A simple eukaryotic model to study aging

The budding yeast *S. cerevisiae*, also known as baker's or brewer's yeast, is a single-celled eukaryotic organism composed of several membrane-bound organelles similar to animal cells including a nucleus, endoplasmic reticulum, Golgi complex, vacuole, cytoskeleton, mitochondria, and other different organelles.³¹ Yeast cells are round to ovoid in shape with a size of ~5 µm in diameter (unbudded cell), between bacteria and human cells in size. Yeast cells divide once every 90 min under optimal laboratory conditions, through a process of budding in which smaller daughter cells detach from their mother cell. The budding yeast was the first eukaryotic organism whose genome was completely sequenced and released in 1996. The haploid yeast cell contains 16 chromosomes comprising about ~12,068 kb of genomic DNA. The genome of yeast is thought to be evolved from the whole-genome duplication of its ancestral set of 8 distinct chromosomes.³² The *S. cerevisiae* yeast genome is composed of many genes that can be grouped into protein-coding genes (5885) and non-coding genes. The budding yeast nuclear genome is composed of more than 6,600 open reading frames (ORFs). The yeast genome is also comprised of 786 dubious ORFs which probably do not encode any proteins. Interestingly, the yeast genome has a very low number of introns, approximately 4% of all genes, as a result of which, the yeast genome is composed of a high number of protein-coding genes (one gene every 2 kbp). The non-coding genes in yeast are transcribed into transfer RNA (tRNA), ribosomal RNA (rRNA), small nuclear RNA (snRNA), and small nucleolar RNA (SnoRNA).³²

The best advantages of yeast as a model are that it is easy to handle, its short generation time, and ease of genetic manipulation. Most interestingly, yeast share several homologous and orthologous genes with mammals including humans, as a result of which yeast can be used even to study human diseases. The budding yeast has long been used as a

model organism for the identification of the molecular basis of several cellular processes including cell cycle, autophagy, protein folding, oxidative stress, and aging. These features make yeast an ideal model organism for the high-throughput screening of identifying genes and chemical compounds associated with aging. However, it is important to note that, its unicellular nature limits its ability to model complex multicellular organisms and tissue-specific aging processes in humans. Additionally, some post-translational modifications that occur in humans do not occur in yeast, and yeast metabolism significantly differs from humans. These features may limit the application of certain findings to human aging research.

Replicative lifespan (RLS) and chronological lifespan (CLS)

Yeast exhibit two distinct patterns of aging such as chronological lifespan (CLS) and replicative lifespan (RLS) (Figure 1). The **Replicative Lifespan (RLS)** measures the mitotic potential of a single yeast cell (*i.e.*, how many bud cells are generated from a single mother cell). Thus, yeast RLS is similar to the mitotic cell division of mammalian cells. For the first time in 1959, Robert Mortimer and John Johnston discovered the aging phenomenon in budding yeast.³³ They reported that yeast cells can divide asymmetrically through mitosis (budding) for a limited number of divisions (~25) and then stop dividing (Figure 1). As the mother cell divides by mitosis, it accumulates molecular damage; however, the daughter cells retain replicative capacity but generally do not inherit such damage from the mother cell. However, some

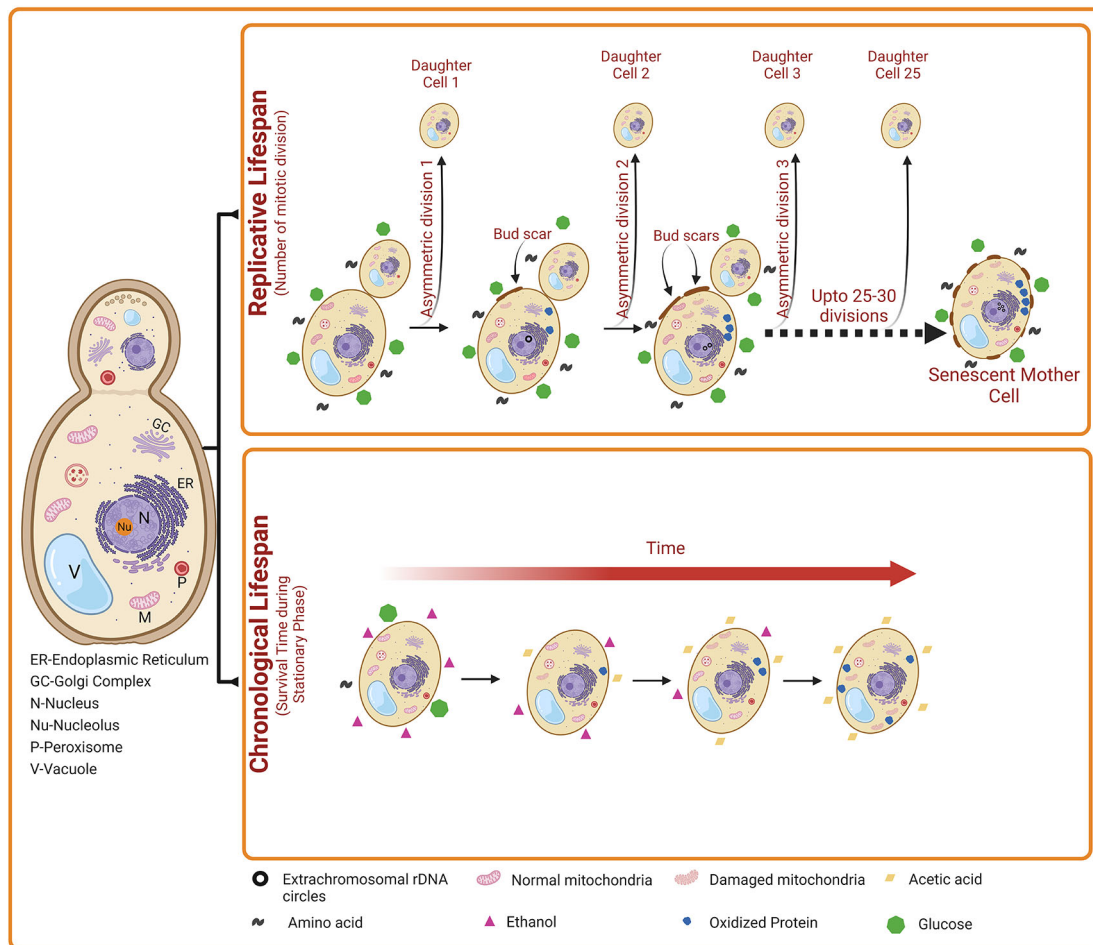


Figure 1. The two aging patterns of *Saccharomyces cerevisiae*. Chronological life span (CLS) indicates the number of days a yeast cell survives in the stationary phase. A gradual decrease in the level of carbon source (e.g., glucose) occurs during stationary phase. Subsequently, ethanol accumulates slowly in the external medium, which is then converted into acetic acid, resulting in the reduction in the pH of the external medium. Elevated acetic acid induces apoptosis of yeast cells. Besides, oxidized proteins and damaged mitochondria also accumulates. Collectively, these events lead to increased cell death with time during yeast Chronological aging. Replicative lifespan (RLS) indicates the number of daughter cells produced by a mother cell. Over time, the accumulation of nuclear extrachromosomal ribosomal DNA circles, oxidized proteins, and damaged mitochondria also occur in the replicatively ageing yeast cells. However, this damage accumulates only in the mother cells but not in the daughter cells.

studies on yeast replicative aging have suggested the asymmetric inheritance of at least three different types of damage, including nuclear extrachromosomal ribosomal DNA (rDNA) circles, oxidatively damaged or misfolded cytoplasmic proteins, and dysfunctional mitochondria (Figure 1).³⁴ Phenotypically, old yeast mother cells are larger in size than the daughters and carry a number of bud scars indicating yeast's RLS. In old mother cells, the actin cytoskeleton is found to be distorted and therefore, mother cells need longer times to complete the cell cycle compared to daughter cells which show a normal dotted and chain-type cytoskeleton. In addition, mother cells also accumulate high levels of mitochondrial-derived reactive oxygen species (ROS) and apoptotic features such as externalization of phosphatidyl serine, nuclear DNA fragmentation and chromatin marginalization.

Accumulation of ERCs is considered as the one of the best characterized and important hall marks of RLS. These ERCs are generated due to homologous recombination within rDNA which leads to the formation of circular DNA molecules with self-replicating capacity. Therefore, molecules or proteins that target rDNA homologous recombination and ERC formation affect the RLS. In yeast, a NAD⁺ dependent histone deacetylase which is encoded by the silent information regulator 2 (SIR2) gene, suppresses ERC formation by inhibiting rDNA homologous recombination. In contrast, the fork block protein (Fob1p) encoded by FOB1 gene promote rDNA recombination and ERCs formation. Therefore, the overexpression of SIR2 or the deletion of FOB1 increases RLS, while deletion of SIR2 gene reduces RLS.³⁵ Although, exact underlying pro-aging mechanisms of ERCs are yet to known, it is speculated that the necessary replication machinery including DNA polymerases, helicase, primase as well as the other transcription factors might interact physically with the accumulating ERCs, resulting in the acceleration of RLS. Another plausible mechanism is increased transcription of rDNA to rRNA, subsequently the imbalance between rRNA and ribosomal proteins ultimately leading to the impaired ribosomal synthesis and function. Also, it is suggested that elevated levels of ERCs induce rDNA stability promoting replicative aging.³⁶

In addition to the prominent role of ERCs in modulating RLS, other factors such as the accumulation of oxidatively modified (i.e., carbonylated) proteins and dysfunctional mitochondria contribute to the progression of replicative aging in yeast. The carbonylated proteins distribute asymmetrically in a Sir2 dependent manner between mother and bud cells, with bud cells not inheriting the oxidized proteins. The daughter cells receive higher levels of undamaged, yet active, cytosolic catalase Ctt1p after cytokinesis, which substantially diminishes ROS levels and attenuates oxidative stress.^{37,38} The beta subunit of mitochondrial F1F0 ATP synthase (Atp2), encoded by ATP2 gene, is essential for the segregation of mitochondria between mother and daughter cells during budding process. Any mutations in ATP2 gene or its deletion not only affects the proper distribution of mitochondria between mother and daughter cells but also induce mitochondrial dysfunction, ultimately influencing the RLS.³⁹ Beside SIR2, RTG2 is another important gene involved in the longevity in yeast. It encodes the Rtg2 (ReTroGrade 2), which acts as a sensor of mitochondrial dysfunction. Rtg2 plays a key role in the mitochondrial retrograde signaling pathway, which relays signals from mitochondria to nucleus. Activation of this pathway by dysfunctional mitochondria leads to changes in nuclear gene expression to restore cellular homeostasis, resulting in the extension of RLS. Deletion of RTG2 enhances the formation of ERCs thereby negative affects the RLS. In contrast, overexpression of RTG2 reduces ERC formation and extends RLS in yeast.⁴⁰

The **Chronological life span (CLS)** measures the yeast cell viability in the non-dividing phase (i.e., postmitotic phase). Thus, CLS is similar to the postmitotic aging of mammalian cells. The CLS is defined as the time duration a yeast cell can survive in a nondividing state (Figure 1), with survival determined by the ability to reenter the cell cycle and resume vegetative growth upon exposure to appropriate growth-promoting cues.^{34,35} Chronological aging is also characterized by the accumulation of protein carbonyl content and dysfunctional mitochondria. In worms, flies and mice, the key regulators of CLS also control RLS and aging. In addition, chronologically aged cells also show a reduction in subsequent RLS, suggesting that similar forms of age-associated damage may contribute to both mitotic (RLS) and postmitotic (CLS) aging in yeast cells.⁴¹ During CLS, the size of yeast cells is normal and they enter a stationary phase due to starvation. The stationary phase cells are characterized by altered cellular metabolism towards the synthesis of reserved carbohydrates such as glycogen and trehalose. During CLS, the starving yeast cells utilize glycogen whereas trehalose is used for membrane stabilization and other non-metabolic functions. In addition, stationary phase cells show a hard and thick cell wall. Stationary phase yeast cells exhibit heterogeneity and can be categorized into quiescent (G0) and non-quiescent cells.⁴² Quiescent cells described as unbudded daughter cells form only during the final cell division in the diauxic phase of the growth curve, and have a high density compared to normal yeast cells. In addition, quiescent cells can reenter synchronously the mitotic cell cycle. In contrast, non-quiescent cells are less dense and composed of heterogenous, asynchronous, and replicatively older cells that lose their division capacity. Non-quiescent cells accumulate elevated ROS levels compared to quiescent cells and exhibit apoptotic as well as necrotic features. After a longer time, the quiescent cells also start to show landmarks of apoptosis, and finally of necrosis.⁴² Though the phenotypes of replicatively older yeast cells (in RLS) and stationary phase yeast cells (in CLS) are different, features such as augmented levels of ROS and intracellular oxidative stress, apoptosis and necrosis are found to be common.

In a standard CLS experiment, yeast cells are grown in either a synthetic defined medium or a nutrient-rich YPD (yeast extract, peptone, and dextrose) medium with glucose as a carbon source.⁴³ During exponential phase, yeast cells proliferate by fermenting glucose to ethanol, leading to the accumulation of ethanol in the initial growth phase. After glucose is depleted, growth rate decreases as cells temporarily arrest growth to adjust their metabolism from fermentation to the respiration.⁴⁴ This shift in metabolism known as diauxic shift, involves cells slowly using secondary carbon sources like ethanol, which is converted to acetic acid, resulting in the acidification of the growth medium. After the ethanol is depleted, cells stop dividing and enter a quiescent state called the stationary phase.⁴⁵ Studies have demonstrated that adjusting the pH of the growth medium to basic conditions or removing acetic acid from the growth medium can extend CLS.⁴⁶ It was also shown that transferring stationary phase yeast cells to water, instead of allowing them to age in a carbon source depleted medium, can extend CLS.⁴⁷ Additionally, it was also demonstrated that, transferring stationary phase yeast cells to water containing only acetic acid reduce the CLS. These findings suggest that extracellular factors, such as acetic acid and pH of the growth medium, plays a key role in the regulation of CLS.

Both intra and extracellular levels of metabolites play a key role in the modulation of CLS. The key metabolites modulating the CLS include acetic acid, ethanol, glycerol, hydrogen sulfide, trehalose, spermidine, reduced nicotinamide adenine dinucleotide phosphate (NADPH), hydrogen peroxide, amino acids, free fatty acids (FFA), sphingolipids, and diacylglycerol (DAG). However, metabolites such as NADPH, trehalose, sphingolipids, FFA, and DAG can influence CLS only within the cell they were produced. Whereas, metabolites such as glycerol, H₂O₂, amino acids, spermidine, H₂S, acetic acid, and ethanol can influence CLS both within the cell they were generated as well as within other cells in the yeast population.⁴⁷ A set of ligand-specific protein sensors detect changes in the concentrations of these metabolites during chronological aging at certain time points called early and late check points. In early check points, which exist in diauxic and post-diauxic phases, metabolites such as NADPH, glycerol, H₂O₂, amino acids, sphingolipids, and spermidine play essential roles in defining the pace of yeast CLS. In contrast, metabolites such as hydrogen sulfide (H₂S), acetic acid, FFA, and DAG define the pace of chronological aging only at late checkpoints.⁴⁷

Several factors have been reported to play a crucial in modulating lifespan in yeast. Oxidative stress that arises due to imbalance between ROS production and cellular antioxidants, is considered as one of the common factors responsible for the reduction in both CLS and RLS. Previous studies also showed that deletion of antioxidant enzymes can influence the lifespan in yeast. Mutants lacking cytosolic copper zinc superoxide dismutase, Cu-Zn SOD (SOD1) and mitochondrial manganese superoxide dismutase, Mn SOD (SOD2) showed a significant reduction in both CLS and RLS.^{48,49} The *sod1Δsod2Δ* double mutant had shorter CLS and the *sod1Δ* mutant showed comparatively longer CLS than *sod2Δ*.⁴⁸ The deletion of catalases did not affect the lifespan.⁴⁹ Interestingly, the overexpression of SOD1 and SOD2 increased CLS.⁴⁷ Despite several similarities and differences between CLS and RLS, these two aging paradigms are interrelated as RLS decreases in chronologically aged cells.⁵⁰ Additionally, both CLS and RLS are regulated by nutrient sensing signaling pathways.^{51,52}

Conserved nutrient sensing aging regulatory pathways in budding yeast

Though budding yeast exhibits different aging paradigms, two major nutrient sensing pro-aging signaling pathways, such as the TOR-Sch9 and the RAS-AC-PKA pathways (Figure 2), promote aging and early death in both RLS and CLS, thus playing a similar role in both aging paradigms, whereas SIR2 does not.⁴³ In presence of nutrients, these pathways promote yeast cell division and growth, but inhibit the general stress response and autophagy. In contrast, the inhibition or inactivation of these pathways results in the extension of both CLS and RLS in yeast.⁴³

The Ras/Adenylate Cyclase/protein kinase A (PKA) Pathway

RAS genes encode small monomeric proteins called GTPases, which act as signal transducers in all eukaryotes. These Ras proteins are primarily involved in the modulating key cellular processes, including cell growth, proliferation, metabolism, and oncogenic transformation.^{54,55} The yeast genes RAS1 and RAS2 are highly homologous to human ras proto-oncogenes, indicating the evolutionary conservation of the ras gene family. Genetic studies have showed that the RAS2 gene can be functionally interchangeable between yeast and humans.⁵⁶ Mutations in RAS genes have been shown to improve the oxidative stress resistance and increase survival rates in different model systems including yeast, *C. elegans*, drosophila, and mammalian cell lines (e.g., PC12 cells).⁵⁷ Chronological aging experiments first identified and characterized that the survival of yeast *ras2Δ* mutant increase by cent percent compared to wild-type yeast. Additionally, *ras2Δ* mutant cells demonstrated augmented resistance to both heat stress and oxidative stress.⁵⁷

In yeast, Ras 1/2 can directly activate adenylate cyclase (Cyr1), which is encoded by CYR1 gene (Figure 2). In addition to direct activation by Ras 1or 2, the Cyr1 can also be activated by the G protein-coupled receptor Gpr1.⁵⁸ These two activation ways for Cyr1 are induced when glucose is present in the growth medium.⁵⁹ Activated Cyr1, in turn, activates a cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA). In its inactive form, PKA exists as a

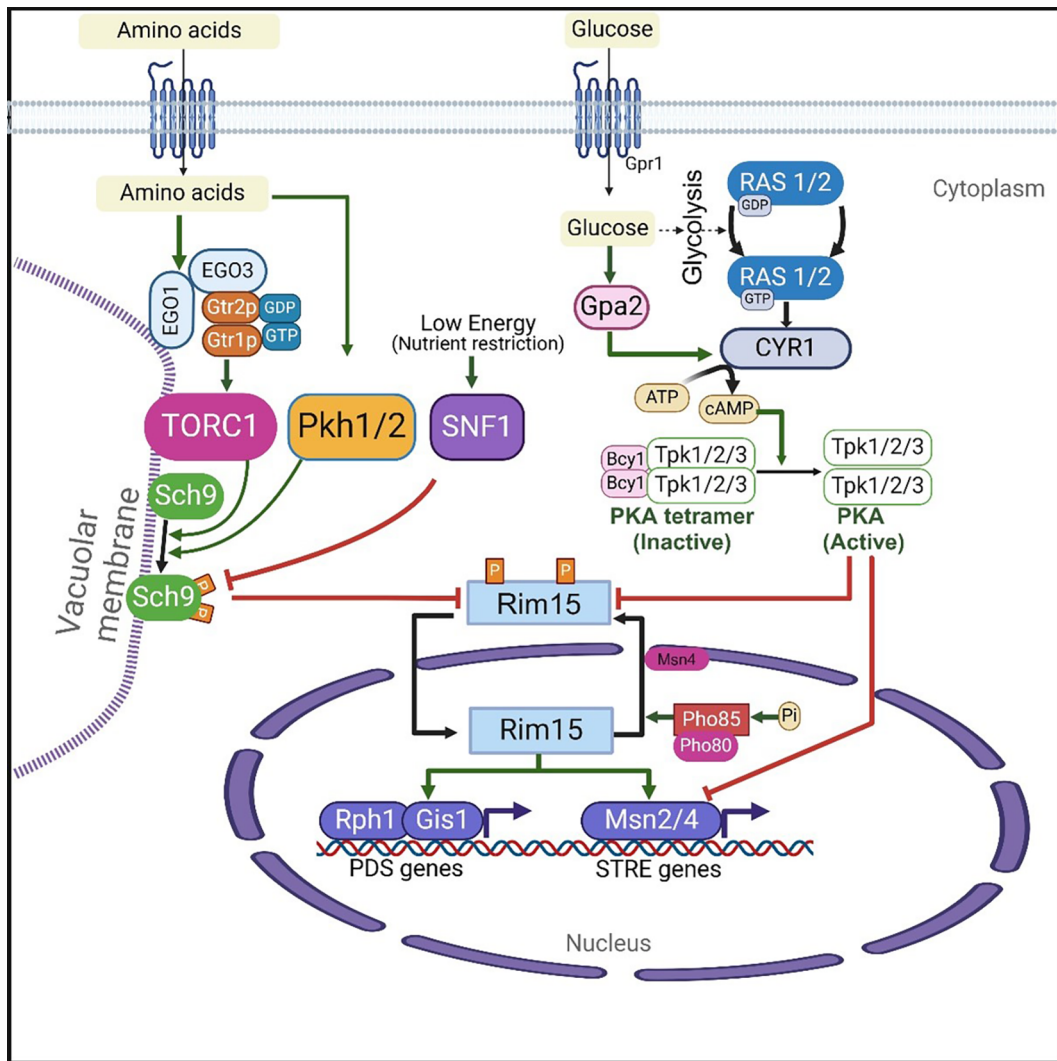


Figure 2. The major nutrient sensing signaling pathways in yeast *Saccharomyces cerevisiae*. Glucose activates adenylate cyclase (CYR1) via stimulation of RAS on one hand and via G protein-coupled receptors (GPCR) system of Gpr1 and Gpa2 on the other hand. The activated adenylated cyclase cause upsurge in the levels of cellular cAMP. Thus, GPR1 and GPA2 are essential for a glucose-dependent rise in the levels of cellular cAMP. Increased intracellular cAMP levels in turn activate protein kinase A (PKA) that exists as a tetramer of two regulatory subunits (Bcy1) and two catalytic subunits (Tpk1, Tpk2 or Tpk3). Binding of cAMP to Bcy1 leads to the dissociation of the tetrameric complex resulting in the activation of the catalytic subunits of PKA. On the other hand, amino acids induced activation of TOR1 is mediated by a heterodimer formed from Gtr1p (orthologue of mammalian Rag A/B GTPase) and Gtr2p (ortholog of mammalian Rag C/D GTPase). The Gtr1p GTP - Gtr2p GDP heterodimer interacts with Ego1 (or Gse2) (an ortholog of the mammalian protein MP1), and Ego3 (or Gse1) (an ortholog of the mammalian protein p14), and forms an EGO/GSE complex. This EGO/GSE complex is localized to the vacuolar membrane via Ego1 subunit. The GTP bound Gtr1p of EGO/GSE complex activates TORC1 which in turn activates Sch9 via phosphorylation. TORC1 can inhibit SNF1 which acts as energy sensor. Both SNF1 and PKH1/2 can influence the activity of Sch9. Both the nutrient sensing pathways RAS-AC-PKA and TORC1-Sch9 converge at Rim15 protein kinase. The activated protein kinases PKA and Sch9 (of RAS-AC-PKA and TORC1-SCH9 signaling pathways) phosphorylates thereby inhibits Rim15 protein kinase activity resulting in the inhibition of its transport to the nucleus. When both PKA and Sch9 are inactive, Rim15 (unphosphorylated form) gets activated and imported to the nucleus, where it induces the activation of transcription factors such as Gis1, Rph1, and Msn2/4. Both Gis1 and Rph1 promotes expression of genes containing postdiauxic shift (PDS) promoter elements. Whereas MSN2/4 induce the transcription of genes containing stress-responsive (STRE) promoter elements. On the other hand, within the nucleus, Rim15 is also inactivated via phosphorylation by a Pho85 cyclin-dependent kinase (in association with its cyclin partner Pho80). Phosphorylated Rim15 is also exported from nucleus to cytoplasm via the Msn5 receptor protein.

tetramer of two regulatory subunits (Bcy1) and two catalytic subunits (Tpk1, Tpk2 or Tpk3) (Figure 2). Although the yeast PKA belongs to a different family of serine/threonine kinase, its two catalytic subunits are 35 to 42% identical to *C. elegans* and human AKT-1/AKT-2.⁶⁰

The binding of cAMP to the regulatory subunits leads to their dissociation from the complex and activation of the catalytic subunits.⁶¹ The activation of PKA is essential for cell growth and proliferation. When glucose is abundant, the Ras/cAMP/PKA pathway gets activated to induce the massive expression of genes that promote growth rate in yeast.⁶² The activated PKA inhibits Rim15, a PAS-kinase that integrates signals from different nutrient sensing signaling pathways such as TORC1, Sch9, PKA, and Pho80-Pho85 to transcription factors Msn2/4 and Gis1 (Figure 2).⁵³ The inhibition of Rim15 phosphorylation positively regulates the transcription factors such as Msn2/4 and Gis1. It is assumed that Rim15 also play a role in the regulation of genes involved in the glucose repression and cell cycle arrest.⁵³ In yeast, the transcription factors Msn2/4 and Gis1 bind respectively to the STRE (STress Responsive Element) and the PDS (post-diauxic shift) sequences, thereby activate stress resistance genes including SOD1 SOD2, CTT1, HSPs, and DDR2 (Figure 2). In contrast, the Ras/cAMP/PKA pathway inactivation leads to enhanced heat stress resistance, by partly activating Msn2 and Msn4, which induce the expression of genes encoding for several heat shock proteins (HSPs), superoxide dismutases (SOD1 and SOD2) catalase (*CTT1*), and the DNA damage inducible gene *DDR2*.^{60,63}

While the critical functioning of Msn2 and Msn4 are vital for the extension of CLs in both *ras2* and *cyr1* mutants, previous studies have also demonstrated the essential role of another transcription factor, Gis1, in enhancing stress resistance and extending CLS under Ras/PKA inactivation.⁶⁴ Thus, the critical roles of Ras/Adenylate Cyclase/PKA Pathway in the regulation of metabolism, stress resistance, proliferation, and longevity in *S. cerevisiae* are mainly linked to the availability of nutrients.⁶³

It was also reported that mutations in *CYR1* gene, as well as mutants with impaired synthesis of cAMP, cause extension of CLS in yeast,⁶⁰ indicating the potential involvement of PKA as a pro-aging pathway. Research evidences also suggests that the pro-aging role of the Ras/adenylate cyclase/PKA pathway seems to be conserved from yeast to mammals. Studies in mice deficient in p66Shc, a signal transducer that might trigger cell proliferation via Ras activation, demonstrated increased oxidative stress resistance and lived 30% longer than wild type.⁶⁵ Yan et al. further strengthened the critical role of adenylate cyclase (AC5) in the regulation of mammalian aging. They reported that both myocytes and fibroblasts isolated from AC5 knock out mice showed enhanced oxidative stress resistance compared to control cells. Additionally, tissues from AC5 knock out mice, such as brain, heart, and kidneys, showed elevated levels of MnSOD and these mice lived 30% longer than their control littermates, implying the fundamental role of adenylate cyclase AC5 in regulating mammalian lifespan and oxidative stress resistance.⁶⁶

Enns et al. (2009) provided evidence for the highly conserved pro-aging role of PKA in mammals though experimental studies in *RIIB* null mice. In mammals, the cAMP dependent-protein kinase A is composed of two regulatory (RI and RII) subunits and two catalytic (C) subunits. The RI and RII subunits exist as two isoforms called *RIα*, *RIβ*, *RIIα*, and *RIIβ*.⁶⁷ The *RIIβ* subunit is predominantly expressed in brown and white adipose tissue and in brain, tissues involved in the regulation of energy homeostasis. *RIIβ* null mice showed lean body mass and increased median and maximum lifespan compared to wild type littermates. This further supports the essential role of the PKA pathway in mammalian aging as well.⁶⁸

The TOR-Sch9 pathway

In response to nutrients, particularly, amino acids, the target of rapamycin (TOR) pathway stimulates anabolic processes and represses catabolic processes such as autophagy, to promote cell growth.⁶⁹ Target of rapamycin (TOR), a serine threonine kinase was first identified in the budding yeast *S. cerevisiae*.⁷⁰ *S. cerevisiae* has two TOR protein kinases, Tor1 and Tor2. TOR forms two structurally and functionally distinct complexes: Tor1 containing TOR complex 1 (TORC1) and Tor2 containing TOR complex 1 (TORC2).⁷¹ While TORC1 responds to amino acids, controlling cell growth, protein synthesis, metabolism, autophagy, and aging, TORC2 is implicated in the sphingolipid biogenesis, endocytosis, and actin organization. TORC1 is highly conserved between yeast and mammals.^{72,73} It consists of subunits such as, TOR1 or TOR2 (ortholog of mammalian TOR, mTOR), Kog1(ortholog of RAPTOR, regulatory-associated protein of TOR), and Lst8 (ortholog of mLST8, mammalian lethal with SEC13 protein 8). Only TORC1 is sensitive to the drugs rapamycin, but not TORC2.⁷⁴

The TORC1 pathway is the second major pathway implicated in the regulation of aging in yeast (Figure 2). In response to amino acids levels, Rag GTPases (members of the Ras superfamily) induce activation of mTORC1 signaling in mammals.⁷⁴ The yeast Gtr1p and Gtr2p are orthologous to mammalian Rag A/B and Rag C/D GTPases, respectively. The amino acid induced activation of TORC1 in yeast is mediated by Gtr1p-GTP and Gtr2p-GDP heterodimer, which

interacts with Ego1 (or Gse2) (an ortholog of the mammalian protein MP1), and Ego3 (or Gse1) (an ortholog of the mammalian protein p14), and forms an EGO/GSE complex (Figure 2). This EGOC is localized to the vacuolar membrane via Ego1 subunit. The GTP bound Gtr1p of EGO/GSE complex activates TORC1, which in turn activates its downstream Sch9 protein kinase (a homolog of human ribosomal S6 kinase 1, S6K1) by phosphorylation.⁷⁵

S. cerevisiae consists of two functionally redundant protein kinases Pkh1 and Pkh2 (homologs of mammalian PDK1, phosphoinositide-dependent protein kinase-1), which are involved in maintaining the cell wall.⁷⁶ Both Pkh 1 and 2 protein kinases can also phosphorylate Sch9 kinase.⁷⁷ In yeast, when glucose levels are low, another protein kinase called SNF1 (sucrose non-fermenting 1 kinase, a homolog of human AMPK) becomes activated and phosphorylate Sch9 (Figure 2), promoting yeast adaptation to glucose depletion. Thus, the yeast AMPK, SNF1 acts as a key regulator of energy homeostasis.⁷⁸

Activation of Tor and Sch9 lead to inactivation of Rim15 kinase and the stress resistance transcription factor Gis1 (Figure 2), both of which are required for maximum CLS extension.⁴³ Similar to Msn2 and Msn4, Gis1 induces the expression of mitochondrial superoxide dismutase enzyme (MnSOD), which is required for the effect of sch9 deletion on CLS. The deletion of *SCH9* can extend both RLS and CLS of yeast.^{60,79,80} Additionally, the combined deletion of *SCH9* along with *RAS2* can furthermore extend the yeast CLS compared to *SCH9* deletion alone.⁸⁰ Both CLS and RLS can be extended by the loss or inhibition of TOR1 via inactivating the downstream Sch9.⁵² Aging yeast is characterized by the elevated levels of ROS. In contrast, reduced levels of ROS were observed in the long-lived mutants deficient in Ras-AC-PKA or Tor-Sch9 signaling.³⁴

During CLS, glucose levels decrease gradually and accumulation of non-fermentable carbon sources such as ethanol and acetic acid takes place. Both ethanol and acetic acid promote the chronological aging in yeast.⁴⁵ Loss of either TOR1 or *SCH9* slows down the aging process partly by lowering respiration and stimulating the exhaustion of ethanol and acetic acid and the elevating the levels of glycerol in the nutrient medium.⁸¹ Since *S. cerevisiae* cannot ferment either acetic acid or ethanol, their depletion by mutations in *TOR* or *SCH9* can prolong the CLS by creating similar conditions usually caused by dietary restriction. It is important to note that the yeast cells deficient in TOR-Sch9 or Ras-AC-PKA signaling pathways exhibit prolonged CLS during incubation in water or in a medium which is either deficient or composed of low amounts of acetic acid and ethanol.^{53,82}

Anti-aging studies of natural products and plant extracts in the budding yeast *S. cerevisiae* as a model

Several genes and genetic pathways involved in aging and lifespan extension have been characterized. Over the last 20 years, researcher have identified anti-aging drugs targeting different age-related pathways/mechanisms, including autophagy inducers, epigenetic regulators, and CR mimetics.⁶ This suggests that targeting both pro-aging and longevity pathways through anti-aging interventions, particularly natural products, contribute significantly to the discovery of natural anti-aging drugs. Natural compounds, which are readily available in food and generally considered much safer for human consumption, serve as one of the main sources of drug discovery and development. Plant derived natural products have been proposed to promote longevity effects through various mechanisms, including 1) maintaining the redox balance, 2) modulating nutrient sensing signaling pathways including the inhibition of mammalian target of rapamycin (mTOR), Insulin/insulin-like growth factor-1 signaling, and nuclear factor- κ B (NF- κ B) signaling pathways, as well as the activation of adenosine 5'-monophosphate (AMP)- activated protein kinase (AMPK) and sirtuins and, 3) regulating autophagy/mitophagy and mitohormesis, 4) regulating gut microbiome, 5) regulating lipid metabolism, 6) removing senescent cells, 7) activating stem cells and their regeneration, and 8) reducing telomere shortening.^{83,84} It is noteworthy that several natural products (e.g., resveratrol, curcumin, spermidine, and curcumin) that demonstrate anti-aging effects in yeast have also entered clinical trials for their potential anti-aging benefits in humans. In the following sections, we have focused mostly on the natural products derived from plants.

Natural products/plant extracts vs. CLS

Several studies indicate that various natural products and plant extracts have the potential to extend CLS in yeast. These natural products belong to different phytochemical classes, such as: flavonoids (e.g., quercetin), carotenoids (e.g., astaxanthin),^{85,86} sesquiterpenes (e.g., artesunate),⁸⁷ triterpenoids (e.g., betulinic acid),⁸⁸ flavanones (e.g., Hesperitin)⁸⁹ and flavonoid glycosides (e.g., Neohesperidin),⁸⁹ polyphenols (e.g., chlorogenic acid),⁹⁰ saponins (e.g., Ginsengoside Rg1),⁹¹ lignans (e.g., Magnolol),⁹² etc. Additionally, crude extracts prepared from different plant species were shown to delay yeast chronological aging. In the following section, we summarize the effects of some natural products and plant extracts on the chronological aging in yeast *S. cerevisiae*. Table 1 lists the natural compounds/plant extracts, their concentrations, phytochemical class, type of growth medium used for CLS experiments, and their anti-aging mechanisms in different *S. cerevisiae* strain backgrounds.

Table 1. List of Natural products/plant extracts extending the chronological lifespan (RLS) in yeast.

Natural Products						
Name	Chemical Class	Dose	Yeast Strain	Yeast Growth Medium	Anti-Aging Mechanism	Ref.
Acetyl-L-carnitine	Amino acid derivative	1 mM	CML39-11A & BY4741	SD	<ul style="list-style-type: none">• ↓ Mitochondrial fission and apoptotic cell death	93
Astaxanthin	Carotenoid	30 μM	BY4741	SD	<ul style="list-style-type: none">• ↓ MDA, ROS, 8-hydroxy-2-deoxyguanosine (8-OHdG) levels• ↑ SOD and GSH levels• ↓ Apoptotic markers	85,86
Artesunate	Sesquiterpene lactone	0.1, 0.5, 5, 25, & 50 μM	BY4743	YPD	<ul style="list-style-type: none">• ↑ Antioxidant defense (Mn SOD)• ↓ ROS• Mimics the effects of CR	87
Betulinic acid	Pentacyclic triterpenoid	30 μM	BY4741	SD	<ul style="list-style-type: none">• ↓ LPO & ROS• ↓ Apoptotic markers	88
Chlorogenic Acid	Polyphenol	5, 10, & 25 μM	DBY746	SDC	<ul style="list-style-type: none">• ↓ ROS, RNS, LPO, PCC, and 8-OHdG• Preserving MMP• ↑ SOD1 and SIR2 mRNA levels	90
4-N-furfurylcytosine	Pyrimidine derivative	0.25, 0.5, & 1.0 mM	BY4741	YPD	<ul style="list-style-type: none">• ↑ mitochondrial respiration• Improved MMP• ↓ ROS levels• ↓ TORC1-Sch9 signaling	97
Galactan	Polysaccharide	300 μg/mL	BY4741	SD	<ul style="list-style-type: none">• ↓ ROS and MDA levels• ↑ SOD activity• ↓ Apoptotic cell death	98
Ginsenoside Rg1	Triterpene saponin	180 g/mL	BY4742	YPD	<ul style="list-style-type: none">• ↑ Antioxidant stress response• ↓ ROS levels and apoptosis• ↑ Mitochondrial bioenergetics and glycolytic enzymes	91
Glutamic acid and methionine	Amino acids	0.2-fold to 5-fold of normal conc.	BY4742	SD	<ul style="list-style-type: none">• Low methionine/glutamic acid ratio in the media increased CLS• High methionine/glutamic acid ratio decreased CLS	99
Hesperitin	Flavonone	0.1, 1, 10, & 100 μM	BY4742	SD	<ul style="list-style-type: none">• ↓ ROS	89

Table 1. *Continued*

Natural Products						
Name	Chemical Class	Dose	Yeast Strain	Yeast Growth Medium	Anti-Aging Mechanism	Ref.
Lithocholic acid	Bile acid	50 μ M	BY4742	YPD	<ul style="list-style-type: none">• Modulation of carbohydrate and lipid metabolism, mitochondrial structure, and function, liponecrotic and apoptotic cell death• Modulating the expression of stress response transcription factors (e.g., Aft1p, Hog1p, Msn2/4p, Rtg1p- Rtg3p, Sfp1p, Skn7p, and Yap1p)	100 ¹⁰³
Magnolol	lignan	20 μ M	BY4741	SCM	<ul style="list-style-type: none">• Regulation of SOD1 and CTA1• Enhanced oxidative stress resistance	92
Morusin and mulberrin	Prenylated flavonoids	60 μ M	BY4742	SD	<ul style="list-style-type: none">• \uparrow Oxidative stress response and• \downarrow Mutation rate• via targeting the SCH9	104
Myricetin	Flavonoid	300 μ M	BY4741	SCM	<ul style="list-style-type: none">• \downarrow ROS and Protein carbonyl levels• \uparrow Oxidative stress resistance	107
Neohesperidin	Flavanone glycoside	0.1, 1, 10, & 100 μ M	BY4742	SD medium	<ul style="list-style-type: none">• \downarrow ROS	89
Quercetin	Flavonoid	300 μ M	BY4741	SCM	<ul style="list-style-type: none">• \downarrow ROS• \uparrow Oxidative stress resistance• \uparrow Acetic acid stress resistance• \downarrow Apoptotic markers	108,109
Spermidine	Polyamine	1 mM	BY4741	SCM	<ul style="list-style-type: none">• \uparrow Deacetylation of histone H3 by inhibiting histone acetyltransferases• \downarrow Oxidative stress and necrosis• \uparrow Autophagy via inducing• \uparrow mRNA levels of ATG1, ATG5, ATG7, and ATG8	110
Sesquiterpene glucosides	Sesquiterpene glucosides	7.5& 10 μ M	K6001	YPGal	\uparrow anti-oxidative stress response	123
Tanshinones	Abietane diterpene	20 nM to 5 μ M	BY4742	SD medium	<ul style="list-style-type: none">• Modulating protein kinases such as Tor1, Sch9, and Gcn2	111

Table 1. Continued

Plant Extracts						
Name	Plant Source	Dose	Yeast Strain	Yeast Growth Medium	Anti-Aging Mechanism	Ref.
Almond extracts	Plant extracts	1 mg/mL	DBY746	SDC	<ul style="list-style-type: none">• ↓ ROS, RNS, LPO, PCC, & 8-hydroxy-2-deoxyguanosine• Preserving MMP• ↑ SOD1 and SIR2 mRNA levels	90
Coffee	Seeds	0.6 mg/mL	BY4741	SDC	<ul style="list-style-type: none">• ↓ ROS levels• ↓ Metabolic activity• ↓ Double DNA-strand breaks	112
<i>Polyalthia longifolia</i>	Extract	1 mg/mL	BY611	YPD	<ul style="list-style-type: none">• ↓ ROS levels• ↑ GSH levels• ↑ mRNA expression of <i>SOD</i> and <i>SIR2</i> genes	113
<i>Nelumbo nucifera</i>	Stamen	0.5 mg/mL	DBY746	SDC	<ul style="list-style-type: none">• ↑ Antioxidant status (both enzymatic activity and gene expression levels of SOD1 and SIRT2)	124
Rice bran extract	Extract	0.001, 0.01, 0.1, 1 mg/mL	BY4742	SD	<ul style="list-style-type: none">• ↓ ROS levels• maintain the plasma membrane integrity• through the modulation of TOR1 and SIR2-dependent pathway	116
<i>Cimicifuga racemosa</i>	Root & rhizome	0.5% (w/v)	BY4742	SD	<ul style="list-style-type: none">• ↓ Pro-aging TORC1 pathway• ↑ Anti-aging SNF1 pathway	118
<i>Valeriana officinalis</i>	Root	0.5% (w/v)	BY4742	SD	<ul style="list-style-type: none">• ↓ Pro-aging PKA pathway	118
<i>Ginkgo biloba</i>	Leaf	0.3% (w/v)	BY4742	SD	<ul style="list-style-type: none">• ↓ inhibitory action of PKA on SNF1	118
<i>Apium graveolens</i>	Seed	0.1% (w/v)	BY4742	SD	<ul style="list-style-type: none">• Stimulating Rim 15 protein kinase	118
<i>Salix alba</i>	Bark	0.1% (w/v)	BY4742	SD	<ul style="list-style-type: none">• ↓ Pro-aging Sch9	118
<i>Salix alba</i>	Bark	0.1% (w/v)	BY4742	SD	<ul style="list-style-type: none">• Remodeling of intracellular and mitochondrial lipid metabolism by• ↓ Intracellular levels of free fatty acids, which results in the postponement of an age-related onset of liponecrotic cell death• ↓ Triacylglycerols and to increase the concentrations of glycerophospholipids within the endoplasmic reticulum membrane, which results in the activation of the unfolded protein response system in the ER, which then decelerates an age-related decline in protein and lipid homeostasis• Changing lipid concentrations in the mitochondrial membranes.	121
<i>Manihot esculenta</i> & <i>Woodyetia bifurcata</i>	Leaf	100 µg/mL	1783	SCM	<ul style="list-style-type: none">• ↑ Oxidative stress response	122

YPD (1% yeast extract, 2% peptone, 2% dextrose); YPGal (1% yeast extract, 2% peptone, 2% Galactose); YPGly (1% yeast extract, 2% peptone, 3% Galactose); SCM (synthetic complete medium); SD (Synthetic defined/synthetic minimal) medium; SDC (synthetic complete dextrose) medium. Symbols ↑ and ↓ indicate up-regulation/increase and down-regulation/decrease, respectively.

Acetyl L-carnitine

Acetyl-L-carnitine (ALC) is an endogenous molecule synthesized in the body from L-carnitine. ALC plays a key role in the energy metabolism and it has been reported to exhibit a plethora of pharmacological properties, including neuroprotective activities. It has also been used as a dietary supplement due to its potent therapeutic effects. Researchers have shown the anti-apoptotic and anti-aging ability of ALC in yeast model. ALC was found to inhibit mitochondrial fission and subsequently improve mitochondrial functioning. Yeast gene MCA1 encodes a Ca²⁺-dependent protease which plays a key role in the regulation of apoptosis. It was found that the mitoprotective effects of ALC were mediated through the yeast metacaspase (Yca1) and thus to its anti-apoptotic activity. ALC was also shown to extend the CLS of yeast cells.⁹³

Astaxanthin

Astaxanthin is a carotenoid compound with superior antioxidant ability than many other natural antioxidant molecules. Sudarshan *et al.* conducted a study to test the antioxidant, anti-apoptotic and anti-aging properties of astaxanthin using yeast model. Astaxanthin treatment prevented oxidative stress-induced surge in MDA and ROS levels and reduction in superoxide dismutase and glutathione levels, thereby increasing the percentage viability of antioxidant gene-deleted yeast mutants by 20-40%. In addition, astaxanthin also prevented the apoptosis of aged cells and subsequently increased the viability of yeast cells during the CLS. Astaxanthin's antioxidant and anti-apoptotic effects are the possible reason for its anti-aging activity.⁸⁵ It was also suggested that anti-apoptotic effects of astaxanthin are also due to its ability to prevent nuclear fragmentation and chromatin condensation in yeast cells.⁸⁶ Sudarshan *et al.* also found that astaxanthin improved oxidative stress resistance and increased the viability of yeast DNA damage repair gene-deleted mutant cells. Astaxanthin was shown to prevent the accumulation of endogenous DNA damage marker (8-hydroxy-2-deoxyguanosine) levels in yeast cells. The anti-aging effects of astaxanthin were also suggested to be due to its ability to inhibit the accumulation of mutation during chronological aging of DNA damage repair gene-deleted mutant yeast cells.⁸⁶

Artesunate

Artesunate is a semi-synthetic derivative of the antimalarial drug artemisinin. Previous studies have shown that artesunate exerts anti-aging effects similar to caloric restriction, indicating the CR mimetic effects of artesunate. From the whole-transcriptome profile analysis studies, it was revealed that artesunate mimics CR-triggered nitric oxide to induce antioxidant defense systems, thereby preventing ROS accumulation and mitigating oxidative stress, subsequently extending yeast lifespan.⁸⁷

Betulinic acid

Betulinic acid (BA) is a pentacyclic triterpenoid present in some plant species. A recent study reported that betulinic acid extends the CLS of yeast cells by mitigating oxidative stress-induced apoptosis. The anti-aging effects of betulinic acid were found to be mediated by the induction of genes associated with heat shock stress response and autophagy.⁸⁸

Citrus flavonoids

Flavonoids have been reported to exert a plethora of pharmacological activities including antioxidant, anti-inflammatory, anti-cancer, anti-neurodegenerative, anti-aging, among others. Researchers have investigated the anti-aging effects of citrus flavonoids including naringin, hesperedin, hesperitin, and neohesperidin on the chronological aging of yeast. Among the tested flavonoids, neohesperidin significantly prevented accumulation of ROS and extended the chronological life span of yeast in a concentration-dependent manner.⁸⁹ In another study, treatment with hesperidin significantly induced the expression levels of SOD and sirtuin2 (SIR2) and prevented ROS accumulation in yeast. In yeast, *UTH1* gene encodes Uth1p, which is activated by oxidative stress, senescence, and TOR-dependent autophagy; all these events subsequently lead to cell death in yeast. Pretreatment with hesperidin, but not its aglycon hesperetin, significantly inhibited the expression of *UTH1* gene, thereby extending yeast lifespan.⁹⁴

4-N-furfurylcytosine

Previous studies have demonstrated that purine and pyrimidine derivatives can exhibit promising health promoting effects.^{95,96} Pawelczak *et al.* investigated the antiaging effects of 4-N-Furfurylcytosine (FC), a cytosine derivative using model *S. cerevisiae*. They found that treatment with FC increased the percentage viability of yeast cells during CLS in a concentration-dependent manner. In addition, treatment with FC boosted the mitochondrial activity and reduced intracellular levels of ROS. It was also demonstrated that FC could limit TORC1 signaling in yeast. This points to the fact that FC's anti-aging activity is through the inhibition of TOR signaling pathway.⁹⁷

Galactan exopolysaccharide

A recent study using yeast models investigated the antioxidant and anti-aging properties of galactan exopolysaccharide isolated from a gram-positive *Weissella confusa*. Galactan exopolysaccharide was shown to prevent the oxidative stress

induced rises in ROS levels and enhance the viability of yeast cells exposed to hydrogen peroxide as an oxidant used in this study. In addition, galactan exopolysaccharide treatment significantly increased the viability of both wild type and antioxidant gene-deleted mutant (*sod2Δ*). The study suggested that the antioxidant potential of the galactan exopolysaccharide could be the possible reason for its anti-aging activity.⁹⁸

Ginsenosides

Ginsenosides are major pharmacological compounds that are unique to the plant species *Panax ginseng* C. A. Meyer (ginseng). Ginsenosides have been demonstrated to extend the life span of different model organism. In a recent study, researchers treated yeast cells with ginsenoside Rg1 and found an augmented antioxidant stress response and concomitant reduction in ROS levels and apoptosis, thereby increasing the viability during aging in yeast model. It was also demonstrated that ginsenoside Rg1 treatment resulted in increased mitochondrial bioenergetics and glycolytic enzymes, thereby improving metabolic homeostasis and delaying aging in *S. cerevisiae*.⁹¹

Glutamic acid and methionine

A study⁴³ reported that the composition of amino acids in aging media can affect the chronological life span of yeast cells. The presence of non-essential amino acids methionine and glutamic acid have been reported to greatly influence the survival rate of yeast cells during aging. Precisely, low levels of methionine and high levels of glutamic acid in the yeast nutrient media led to extended lifespan in yeast model. In contrast, increasing levels of methionine and reducing levels of glutamic acid caused a decrease in yeast life span. Therefore, it can be concluded that amino acid composition is a critical factor for controlling yeast aging.⁹⁹

Lithocholic acid

Previous studies have reported that lithocholic acid, a bile acid, can increase yeast cell survival during chronological aging.^{100–103} Interestingly, lithocholic acid was also shown to significantly enhance the survival rate of yeast especially under caloric restriction conditions. Lithocholic acid treatment was shown to modulate several cellular pathways, including carbohydrate and lipid metabolism, mitochondrial structure and function, liponecrotic and apoptotic cell death of yeast during chronological aging.¹⁰⁰ It is important to note that lithocholic acid's anti-aging effects under caloric restriction are found to be prominent only when this compound is added to the growth medium either at logarithmic/diauxic and early stationary stages of yeast aging. Addition of lithocholic acid either at logarithmic/diauxic and early stationary stages induced the activation of several longevity related cellular processes which ultimately triggering the enhanced yeast cell survival during aging.¹⁰¹ Beach *et al.* also demonstrated that lithocholic acid exerts its anti-aging effects through the modulation of the expression of different transcription factors including Aft1p, Hog1p, Msn2/4p, Rtg1p- Rtg3p, Sfp1p, Skn7p, and Yap1p. Each of these transcription factors in turn alter the levels of several intra and extra mitochondrial proteome, and subsequent maintenance of mitochondrial function. Altogether, Beach *et al.* suggested that lithocholic acid's anti-aging effects are mainly through the modulation of aging-related transcriptional landscape.¹⁰² Also, it was discovered that lithocholic bile acid accumulates in mitochondria, and alters the mitochondrial membrane lipidome which is crucial for the restoration of mitochondrial proteome, subsequently an improved mitochondrial function and increased chronological aging by lithocholic acid.¹⁰³

Magnolol

In our previous study, we reported the anti-aging effects of magnolol, a natural polyphenol. Magnolol enhanced the stress resistance of yeast cells exposed to hydrogen peroxide, an oxidizing agent. In addition, magnolol increased the viability of the short-lived yeast mutant *sod1Δ*, which lacks the antioxidant enzyme superoxide dismutase. Our study suggested that the anti-aging effects of magnolol occur mainly through the modulation of oxidative stress during yeast chronological aging.⁹²

Morusin and mulberrin

Mulberry leaves are rich in flavonoids such as morusin and mulberrin, and these have been demonstrated to enhance the survival rate during yeast chronological aging. It was also found that morusin and mulberrin exert their anti-aging effects via targeting the SCH9, a major target of TORC1 in budding yeast *S. cerevisiae*.¹⁰⁴ Budding yeast Sch9 is the major substrate of the TORC1. Yeast Sch9 functions analogously to S6K1, the mammalian TORC1 substrate. Yeast TORC1 phosphorylates about six amino acid residues of Sch9, indicating that the TORC1-dependent phosphorylation of Sch9 is essential for its activity.¹⁰⁵ Activated Sch9 plays a key role in the regulation of several cellular processes including protein synthesis (via modulating ribosome synthesis and translation initiation), cell cycle, and aging. Deletion of SCH9 causes growth defects such as reduction in cell size and growth rate; however, deletion of SCH9 leads to enhanced temperature tolerance as well chronological and replica life spans in budding yeast. The longevity-extending effects due to SCH9 deletion are explained by the augmented oxidative stress response and reduction in age-associated mutation rate.¹⁰⁶

Myricetin

In another study, using budding yeast as a model, researchers investigated antioxidant and anti-aging effects of myricetin, a polyphenolic flavonoid compound which is composed of a pyrogallol ring in the B ring of its structure. Myricetin's antioxidant effects are attributed to the presence of a hydroxyl group in its B ring. Treatment with myricetin reduced the levels of ROS and protein carbonyl content, thereby enhancing the oxidative stress resistance of yeast cells exposed to hydrogen peroxide. Myricetin was found to inhibit H₂O₂-induced glutathione oxidation, but did not enhance endogenous antioxidant enzymatic activity in yeast. Additionally, myricetin treatment significantly prevented age associated oxidative stress and extended the CLS of yeast mutant lacking mitochondrial superoxide dis-mutase (*sod2Δ*).¹⁰⁷

Quercetin

It is noteworthy that several of the yeast genes, such as, PEP4 and TEL1, share homology with human genes of diseases relevance, such as CTSD and ATM, respectively.^{108,109} In a previous study, we demonstrated the protective effects of quercetin on *S. cerevisiae pep4Δ* mutant that lack the *PEP4* gene encoding a vacuolar endopeptidase proteinase A. This vacuolar proteinase A is a homolog of the human cathepsin D (encoded by CTSD), which plays a key role in the normal development and maintenance of neurons in the central nervous system. Particularly, it is essential for the degradation of proteins linked to several neurodegenerative diseases such as Parkinson's disease, Huntington disease, neuronal ceroid lipofuscinosis, and Alzheimer's disease.¹⁰⁸ Yeast *pep4Δ* cells are found to be highly sensitive to oxidative and apoptotic stressors. However, in our study, we demonstrated that quercetin treatment reduced ROS levels and apoptotic markers, thereby increasing the percentage viability of yeast *pep4Δ* cells during chronological aging.¹⁰⁸

The mammalian serine/threonine protein kinase ATM plays an important role in DNA damage sensitivity, cell cycle checkpoint deficiency, cancer incidence and telomere length maintenance. Mutation in ATM gene is linked to elevated oxidative damage, premature aging, and apoptosis. In another study, we also investigated the protective effects of quercetin on the sensitivity of *S. cerevisiae tell1Δ* cells lacking Tel1p, which is a homolog of the human ATM (Ataxia Telangiectasia Mutated) gene mutation. Our study results showed that quercetin treatment prevented ROS accumulation and thereby enhanced the stress resistance of *tell1Δ* cells exposed to a variety of oxidizing agents. Furthermore, treatment with quercetin prevented apoptotic death of yeast *tell1Δ* cells and increased cell viability during chronological aging.¹⁰⁹

Spermidine

Spermidine has been reported to inhibit histone acetyltransferases and subsequent deacetylation of histone H3, thereby preventing oxidative stress and necrosis in yeast aging. On the contrary, reduction of endogenous polyamines caused hyperacetylation, accumulation of ROS, necrotic cell death and a diminished life span. It is important to note that treatment with spermidine causes alteration in acetylation status of the chromatin, resulting in a substantial increase in the autophagy in different model organisms, including yeast. This suggests that spermidine's anti-aging effects are mediated through its ability to stimulate the autophagy pathway.¹¹⁰

Tanshinones

Wu *et al.* found that the dried roots of *Salvia miltiorrhiza* Bunge have substantial longevity extending effects. They reported that tanshinones (*e.g.*, cryptotanshinone, tanshinone I, and tanshinone IIa) are pharmacologically active components present in the roots of *S. miltiorrhiza*. Precisely, cryptotanshinone has been reported to extend the CLS of yeast wild type as well as yeast mutant lacking mitochondrial superoxide dismutase (*sod2Δ*). Their study suggests that the cryptotanshinone-induced anti-aging effects are modulated through the involvement of nutrient-sensing protein kinases such as Tor1, Sch9, and Gcn2.¹¹¹

Almond extracts

Almond (*Prunus dulcis* (Mill.) D.A. Webb) is a major nut crop worldwide. Multiple health benefits associated with the consumption of almonds are due to the phenolic-rich almond skin. Previous studies have found that pre-treatment with almond skin extract and chlorogenic acid significantly extended the lifespan of yeast. Both almond extract and chlorogenic acid improved the mitochondrial function during chronological aging of yeast cells by reducing the accumulation of free radicals (including ROS and RNS) and preserving mitochondrial membrane potential (MMP). Furthermore, treatment with almond extract and chlorogenic acid augmented the oxidative stress response by inducing the expression levels of *SIR2* and *SOD1* genes and decreasing the endogenous levels of lipid peroxides, protein carbonyls and 8-hydroxy-2-deoxyguanosine (8-OHdG) in yeast cells. Altogether, it can be suggested that the longevity-extending effects of almond extract are ascribed to its ability to ameliorate oxidative stress in yeast cells.⁹⁰

Coffee

Czachor, J., *et al.* demonstrated the lifespan-extending effects of coffee infusions in *S. cerevisiae*. Coffee, especially the *Coffea robusta* type, was found to exhibit superior antioxidant effects than the *Coffea arabica* type, thereby protecting cells from ROS-induced DNA damage and additionally improving the metabolic activity in yeast cells. overall, it can be

suggested that coffee exhibits health benefits mainly through the reduction of ROS accumulation and the enhancement of metabolic activity.¹¹²

Polyalthia longifolia

Polyalthia longifolia is a polyphenol-rich traditional medicinal plant that has long been used for its rejuvenation capacity. *P. longifolia* has been reported to exhibit potent pharmacological activities including antioxidant and hepatoprotective activities. A previous study,⁶³ tested the anti-aging activity of methanolic leaf extract of *P. longifolia* using yeast CLS model and found that the methanolic leaf extract enhanced the viability of yeast cells and extended the CLS of yeast. It was reported that methanolic leaf extract significantly prevented the accumulation of H₂O₂-induced ROS levels and increased GSH levels. Furthermore, treatment with methanolic leaf extract strikingly induced the expression levels of *SOD* and *SIRT1* genes. Overall, it can be suggested that *P. longifolia* exerts its anti-aging effects through the modulation of oxidative stress response and *SIRT1* gene.¹¹³ It was also reported that methanolic leaf extract of *P. longifolia* extended the RLS of yeast via ameliorating the apoptotic features of replicatively ageing yeast cells.¹¹⁴

Rice bran extract

Pigmented rice is the functional food in many countries including India, China, and Japan, and it is the richest source of polyphenols.¹¹⁵ It has been reported that red rice bran extract can prevent the accumulation of ROS levels, maintain plasma membrane integrity and extend the CLS of yeast cells. The anti-aging mechanism of action of rice bran extract is through the modulation of the TOR1 and SIR2-dependent pathways.¹¹⁶

Sacred lotus stamen extract

The stamen of lotus (*Nelumbo nucifera*) is rich in flavonoids and has long been widely used in Indian traditional medicine. Tungmunnithum *et al.* reported that treatment with lotus stamen extract significantly enhanced the antioxidant status (both enzymatic activity and gene expression levels of *SOD1* and *SIRT2*) and extended the CLS of yeast cells. Interestingly, the longevity extending effects of lotus stamen extract were reported to be superior to the resveratrol treatment.¹¹⁷

Previous studies also demonstrated that a variety of plant extracts can extend the CLS in yeast by modulating both pro-aging and anti-aging protein kinases. Plants extracts of *Apium graveolens* and *Cimicifuga racemosa* have been shown to stimulate the anti-aging protein kinases Rim15 and SNF1, respectively.¹¹⁸ Both *Valeriana officinalis* and *Ginkgo biloba* extracts were shown to exert inhibitory action on the pro-aging PKA pathway, whereas, the anti-chronological aging effects of *Cimicifuga racemosa* and *Salix alba* were shown to be modulated via inhibitory action on the pro-aging kinases Sch9 and TORC1, respectively.¹¹⁸

The anti-aging potential of these plant extracts were also attributed to their ability to enhance hormetic stress response in yeast. Precisely, these extracts were shown to increase mitochondrial respiration and membrane potential, decrease or increase ROS, enhance resistance to both thermal and oxidative stress, and mitigate oxidative damage to protein, lipids, and DNA.^{119,120} Additionally, *Salix alba* extract was demonstrated to exhibit anti-chronological aging effects via remodeling of both intracellular and mitochondrial lipid metabolism, particularly, by decreasing intracellular free fatty acid levels, resulting in delay in the age-related liponecrotic yeast cell death.¹²¹ Kwong, M.M.Y. *et al.* (2021) screened for the anti-aging potential of 222 plant extracts and their findings revealed that two plant extracts namely *Manihot esculenta* and *Wodyetia bifurcata* could extend the CLS via inducing the oxidative stress response pathways in yeast.¹²²

Natural products/plant extracts vs. RLS

Researcher also demonstrated the potential of natural products and plant extracts to extend the RLS in yeast. These natural products belong to different phytochemical classes, such as secoiridoid glycoside (e.g., amarogentin),¹²⁵ flavonone glycoside (e.g., hesperidin),⁹⁴ triterpenoid glycoside (e.g., cucurbitane glycoside),¹²⁶ ergosterol derivatives (e.g. ganodermasides A and B),¹²⁷ phospholipid (e.g., lysophospholipid),¹²⁸ flavonoid (e.g., phloridzin),¹²⁹ stilbenoid (e.g., resveratrol),¹³⁰ and polyphenolic glycosides (e.g., parishin).¹³¹ Others also demonstrated that crude extracts prepared from different plant species including *Polyalthia longifolia*,¹¹⁴ *Psoralea corylifolia*,¹³² and *Pterocarpus marsupium*¹³³ extended RLS in yeast. In the following section, we summarize the effects of some natural products and plant extracts on the replicative aging in yeast *S. cerevisiae*. Table 2 lists the natural compounds/plant extracts, their concentrations, phytochemical class, type of growth medium used for RLS experiments, and their anti-aging mechanisms in different *S. cerevisiae* strain backgrounds.

Amarogentin

Disasa *et al.* isolated a secoiridoid glycoside amarogentin from a Chinese traditional medicinal plant, *Gentiana rigescens* Franch. Amarogentin was reported to enhance both the enzymatic activities and expression levels of superoxide

Table 2. List of Natural products/plant extracts extending the replicative lifespan (RLS).

Natural Products							Ref.
Name	Chemical Class	Dose	Yeast Strain	Yeast Growth Medium	Anti-Aging Mechanism		
Amarogentin	Secoiridoid glycoside	1, 3 and 10 μ M	K6001	YPGal	<ul style="list-style-type: none">• \uparrow SOD, CAT, and GPx activities• \uparrow mRNA levels of SOD1 and SOD2, CAT, and GPx activities		125
Hesperidin	Flavanone glycoside	5, 10, and 50 μ M	K6001	YPGal	<ul style="list-style-type: none">• \uparrow SOD1, UTH1, and SIR2 mRNA levels• \downarrow ROS		94
Cucurbitane glycoside	Triterpene glycoside	1, 3, and μ M	K6001	YPGal	<ul style="list-style-type: none">• \downarrow ROS levels• \downarrow mRNA levels of UTH1 and SKN7• \uparrow mRNA levels of SOD1 and SOD2		126
Copper sulfate	Inorganic compound	62 μ M	W303-1A, S288c, BY4742, SP-22	YPGly	<ul style="list-style-type: none">• \uparrow Respiratory metabolism• Activation of stress response genes• Improved mitochondrial function		137,138
Ferric chloride	Inorganic compound	1 mM	BY4742	YPGly	<ul style="list-style-type: none">• Activation of multicopper oxidase enzyme Fet3p• \downarrow ROS levels• \uparrow mRNA levels of genes related to the mitochondrial metabolism (e.g., TCA cycle and electron transport chain)• Elevated levels of ATP• Amelioration of mitochondrial energy metabolism		137-139
Ganodermasides A and B	Ergosterol derivatives	1, 10, and 100 μ M	K6001	YPGal	<ul style="list-style-type: none">• via modulating the expression of UTH gene		127
Isonicotinamide	Amide form of isonicotinic acid	25 mM	BY4741	SCM	<ul style="list-style-type: none">• \uparrow Intracellular levels of NAD⁺ via NAD⁺ salvage pathway• \uparrow Sir2 activation, subsequent increase in silencing at the rDNA locus		144
Lysophosphatidic acid	Bioactive phospholipid	10 and 30 μ M	K6001	YPGal	<ul style="list-style-type: none">• \uparrow oxidative stress resistance• amelioration of antioxidant status and the genes of <i>UTH1</i>, <i>SKN7</i>, and <i>SOD</i>		128
Nicotinamide Riboside	Form of vitamin B3	10 μ M	BY4742	YPD	<ul style="list-style-type: none">• \uparrow NAD⁺ levels via activation of both Nrk1-dependent and Nrk1-independent pathways• \uparrow Sir2-dependent gene silencing		142
Parishin	Polyphenolic glycoside	3, 10, and 30 μ M	K6001	SCGal	<ul style="list-style-type: none">• \uparrow expression of levels of SIR2 and SOD activity,• \downarrow ROS and lipid peroxidation• \downarrow mRNA levels of TOR signaling-related genes (e.g., TORC1, RPS26A, and RPL9A)		131
Phloridzin	Flavonoid	3, 10, and 30 μ M	K6001	YPGal	<ul style="list-style-type: none">• \uparrow mRNA levels of SOD1, SOD2, and SIRT1		129

Table 2. *Continued*

Natural Products						
Name	Chemical Class	Dose	Yeast Strain	Yeast Growth Medium	Anti-Aging Mechanism	Ref.
Rapamycin	Macrolide	200 ng/ml	BY4741	SCM	<ul style="list-style-type: none">• ↓ TORC1 complex• Stabilization of rDNA locus via increased association of Sir2 with ribosomal DNA (rdna)• ↓ Extrachromosomal rDNA circles	148
Resveratrol	stilbenoid	30 μM	W303-1a	SCM	<ul style="list-style-type: none">• ↓ Number of senescent cells with fragmented mitochondria• ↑ Mitochondrial DNA content• ↑ mRNA levels of DNM1 and FZO1 genes• ↓ROS	130
Sesquiterpene glucosides	Sesquiterpene glucosides	7.5 and 10	K6001	YPGal	<ul style="list-style-type: none">• ↑ anti-oxidative stress response	123
Plant Extracts						
Name	Plant Source	Dose	Yeast Strain	Yeast Growth Medium	Anti-Aging Mechanism	Ref.
<i>Psoralea corylifolia</i>	Extract	10 μg/mL	MEP strain ZHY1	YPD	<ul style="list-style-type: none">• Via modulating Tor1• Sir2-independent pathway	132
<i>Polyalthia longifolia</i>	Extract	1 mg/mL	BY611	YPD	<ul style="list-style-type: none">• Amelioration of apoptotic features	114
<i>Pterocarpus marsupium</i>	Extract	100 μg/mL	BY4742	YPD	<ul style="list-style-type: none">• Anti-aging effects might involve alterations in cellular processes related to aging	133

YPD (1% yeast extract, 2% peptone, 2% dextrose); YPGal (1% yeast extract, 2% peptone, 2% Galactose); YPGly (1% yeast extract, 2% peptone, 3% Galactose); SCM (synthetic complete medium); SD (Synthetic defined/synthetic minimal) medium; SDC (synthetic complete dextrose) medium. Symbols '*' and '↓' indicate up-regulation/increase and down-regulation/decrease, respectively.

dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), thereby improving the viability of yeast cells exposed to oxidative stress. Furthermore, treatment with amarogentin resulted in an enhanced RLS of yeast wild type; however, this compound was not shown to extend the lifespan of yeast mutants *sod1Δ*, *sod2Δ*, *uth1Δ*, and *skn7Δ*, suggesting that the anti-aging effects of amarogentin are mainly through the regulation of antioxidative stress as well as by the regulation of *UTH1*, *SKN7*, *SOD1*, and yeast *SOD2* gene expression.¹²⁵

Cucurbitacins

Cucurbitacins are a class of tetracyclic triterpenoids that are abundant in plants belonging to the family Cucurbitaceae. Cucurbitacins have been reported to exhibit strong anticancer activity, and are divided into 12 classes from A to T with over 200 derivatives.¹³⁴ Cucurbitacin B is the most abundant and active member of the cucurbitacins.¹³⁵ Researchers have discovered that cucurbitacin B can extend both replicative and chronological life spans in yeast. Treatment with cucurbitacin B enhanced the lifespan of yeast by promoting the expression of *ATG32*. Cucurbitacin B could not increase the lifespan of yeast mutants devoid of autophagy related genes (*ATG2* and *ATG32*), pointing to the fact that the anti-aging effects of cucurbitacin B are mainly through the induction of autophagy in yeast.

It was also demonstrated that cucurbitacin B can ameliorate oxidative stress levels mainly through the induction of superoxidase dismutase activity (via enhanced expression of *SOD1* and *SOD2*) and the prevention of accumulation of oxidative stress markers including ROS and malondialdehyde (MDA). Furthermore, researchers also showed that the anti-aging effects of cucurbitacin B are also mediated through the regulation of expression of other aging-related genes such as *UTH1* as well as *SKN7*. Cucurbitacin B's anti-aging effects are attributed to its ability to ameliorate oxidative stress and regulate autophagy and age-related genes in yeast.¹³⁶

Additionally, cucurbitane glycoside isolated from the methanol extracts of *Momordica charantia* L. fruits has been reported to significantly extend the RLS of K6001 budding yeast mainly through suppressing ROS levels and the oxidative stress burden. Treatment with cucurbitane glycoside resulted in a decrease in the expression levels of *UTH1* and *SKN7* and an increase in the expression levels of *SOD1* and *SOD2*. However, cucurbitane glycoside was not able to extend the RLS of the yeast mutants *uth1Δ*, *skn7Δ*, *sod1Δ*, and *sod2Δ*, suggesting that cucurbitane glycoside exerts antiaging effects via antioxidative stress and regulation of yeast *UTH1*, *SKN7*, *SOD1*, and *SOD2* gene expression.¹²⁶

Copper and iron supplementation

Previous studies were conducted to demonstrate the effects of supplementation of copper and iron on the yeast RLS. It was found that addition of copper to the growth media increased RLS via the activation of multicopper oxidase enzyme (Fet3p) that works in combination with another enzyme called iron permease (Ftr1p), allowing for high intake of iron into yeast cells. Furthermore, it is important to note that high levels of iron-mediated anti-aging effects are dependent on the multicopper oxidase enzyme. However, the life span-extending effects of both copper and iron occurred in the growth medium supplemented with only glycerol as a carbon source but not glucose.

It was also demonstrated that supplementation of either copper or iron prevented the accumulation of ROS levels, thereby enhancing the replicative life span of yeast mutants lacking antioxidant enzymes.^{137,138} The iron-mediated anti-aging effects occur mainly through the enhanced expression of genes related to the mitochondrial metabolism especially tricarboxylic acid (TCA) cycle and electron transport chain, subsequently elevating levels of adenosine triphosphate (ATP), which is essential for increased survival cells during aging. Interestingly, supplementation of iron could also enhance the life span of yeast *Snf1Δ* mutant which lacks SNF1/AMPK protein kinase. Therefore, it can be suggested that the iron's life span-extending effects occur via amelioration of mitochondrial energy metabolism in yeast.¹³⁹

Ganodermasides A and B

Medicinal mushrooms have been reported to exhibit anti-aging activity. In a study,³⁸ researchers isolated two ergosterol derivatives, namely ganodermasides A and B, from the spores of the medicinal mushroom *Ganoderma lucidum*. They showed that both ganodermasides A and B could extend the replicative life span of *S. cerevisiae* through the modulation of the expression of *UTH1*. In yeast, different transcription factors such as Skn7, Yap1, and Mot3 play a crucial role in oxidative stress resistance. It was suggested that upon phosphorylation, these transcription factors get activated, thereby regulating the expression of *UTH1* gene by binding to its upstream promoter region. It was reported that polyphenols' anti-aging activity occurs through the activation of Skn7 and subsequent increased expression of the *UTH1* gene.¹²⁷

Lysophosphatidic acid

In another study, Sun Y *et al.*, isolated lysophosphatidic acid (LA) from the seeds of *Arabidopsis thaliana* and showed that LA augmented oxidative stress resistance, thereby promoting the extension of RLS in yeast. However, LA was not able to extend the replicative lifespan of mutants *uth1Δ*, *skn7Δ*, *sod1Δ*, and *sod2Δ*. This study suggests that LA's

anti-aging effects are possibly through the amelioration of antioxidant status of yeast cells and the genes of *UTH1*, *SKN7*, and *SOD* may also be involved in the action.¹²⁸

Nicotinamide adenine dinucleotide (NAD+) precursors

Alterations in the biosynthesis and regulation of nicotinamide adenine dinucleotide (NAD+) plays a crucial role in the progression of aging as well as pathophysiology of several age-related chronic diseases.¹⁴⁰ NAD+ plays a crucial role in several metabolic processes in the cells. Most importantly, NAD+ functions as a co-factor in redox reactions and it is reduced to NADH in many metabolic pathways including glycolysis, the citric acid cycle, and fatty acid metabolism. Adequate intracellular levels of NAD+ are maintained through the combined action of NAD(+) biosynthesis and salvage pathways.

Several key cellular enzymes including sirtuin protein deacetylases and poly-ADP-ribose polymerases (PARPs) are NAD+ dependent, and use NAD+ as a substrate in many cellular processes, including aging. Aging is associated with a reduction in NAD+ levels, leading to alterations in several metabolic processes that are NAD+-dependent, which in turn leads to the ageing-associated physiological/functional decline. Therefore, supplementation with diets rich in three important NAD+ precursors 1) nicotinamide, 2) nicotinic acid (*e.g.*, protein rich foods such as cereals, peanuts, meat, fish) and 3) nicotinamide riboside (*e.g.*, milk, cabbage, cucumber) ameliorate age-related decline in NAD+ levels and help in the extension of active longevity.¹⁴¹

Nicotinamide riboside is a natural product present in milk.³⁰ NAD+ is also required for the proper functioning of Sir2 and extension of RLS in budding yeast. Alterations in NAD+ levels negatively affect the RLS of yeast. In eukaryotes, nicotinamide riboside kinases (Nr1 and Nr2) catalyze the phosphorylation of nicotinamide riboside to nicotinamide mononucleotide, the precursor of NAD+. A previous study reported that the supplementation of nicotinamide riboside increased the levels of NAD+ via activation of both Nr1-dependent pathway and the Urh1/Pnp1/Meu1 pathway (an Nr1-independent pathway).

Increased NAD+ levels in turn lead to enhanced Sir2-dependent gene silencing, thereby extending RLS in yeast.¹⁴² The Sir2 enzyme deacetylates the lysine residues of histones, thereby silence all heterochromatin-like regions including telomeres, rDNA, and the hidden mating type loci HML/HMR (Hidden MAT Left/ (Hidden MAT Right)).¹⁴³ In the *S. cerevisiae* NAD+ salvage pathway, nicotinamide is recycled from NAD+ by the Sir2 mediated deacetylation reaction.

The nicotinamidase (Pnc1) catalyzes the conversion of nicotinamide to nicotinic acid, which is further converted to nicotinamide mononucleotide by the enzyme nicotinamide phosphoribosyltransferase (Npt1). Isonicotinamide (a compound similar in shape and electrical properties to nicotinamide) was shown to elevate intracellular levels of NAD+ through the yeast NAD+ salvage pathway, leading to an increase in Sir2 activation. This, in turn, enhance normal silencing at the rDNA locus in yeast and extension of yeast RLS.¹⁴⁴

Parishin

Parishin is a phenolic glucoside isolated from *Gastrodia elata*, a Chinese traditional medicinal plant. Treatment with parishin significantly increased cell viability under oxidative stress and extended the replicative life span of K6001 yeast. Parishin treatment significantly induced the expression of levels of SIR2 and SOD activity, while preventing the accumulation of ROS and lipid peroxidation. However, Parishin did not increase the RLS of *sod1Δ*, *sod2Δ*, *uth1Δ*, and *skn7Δ* mutants of K6001 yeast.

Treatment with parishin suppressed the expression of several TOR signaling pathway-related genes such as TORC1, ribosomal protein S26A (RPS26A), and ribosomal protein L9A (RPL9A). In addition, parishin significantly diminished the gene expression levels of *RPS26A* and *RPL9A* in *uth1Δ* mutant, as well as in *uth1 Δsir2Δ* double mutants. Also, parishin remarkably suppressed the TORC1 gene expression in *uth1* mutants. These study results indicate that parishin exerts its anti-aging activities by modulating Sir2/Uth1/TOR signaling pathway.¹³¹

Phloridzin

Xiang, L. *et al.*, investigated the anti-aging effects of apple polyphenol, phloridzin, using yeast RLS model. Phloridzin treatment significantly increased the percentage viability of yeast cells exposed to hydrogen peroxide. It was also demonstrated that phloridzin treatment led to increased expression of SOD1/2 and SIRT1 genes as well as the activity of superoxide dismutase enzyme. Altogether, it was suggested that the anti-aging effects of phloridzin are mediated through the regulation of expression of SIRT1 in budding yeast.¹²⁹

Rapamycin

Eukaryotic cells growth and proliferation is regulated by an evolutionarily conserved kinase, the target of rapamycin (TOR). It has been shown that the inactivation of TOR signaling pathway leads to lifespan extension in different eukaryotic model organisms. The eukaryotic nucleolus is rich in ribosomal DNA (rDNA) that is composed of multiple tandem repeats of rRNA genes (100-200 copies rDNA repeats) and the components for ribosome assembly. Inside the nucleolus, the transcription of rDNA produces precursor rRNA that in turn will be processed further and become associated with ribosomal proteins to form preribosomal subunits.

Sir2 is a histone deacetylase enzyme involved in silencing the transcription at the rDNA locus to enhance yeast life span.^{145,146} Nearly 50% of the rDNA repeats are maintained in a silent state partly by the Sir2 protein.¹⁴⁷ Using *S. cerevisiae* yeast as model, it was found that rapamycin treatment cause inhibition of the TORC1 complex, resulting in the increased association of Sir2 with ribosomal DNA (rDNA) in the nucleolus. This association of SIR2 with rDNA reduces homologous recombination between rDNA repeats that causes formation of toxic extrachromosomal rDNA circles. Thus, rapamycin treatment-induced TORC1 inhibition signals the stabilization of rDNA locus by promoting the association of Sir2 with rDNA, thereby extending the RLS in *S. cerevisiae*.¹⁴⁸

Resveratrol

Mitochondrial dynamics, the balance between mitochondrial fission and fusion, is critical for cell growth and functioning. Replicative senescence in yeast is characterized by the presence of fragmented mitochondria due to mitochondrial fission rather than fusion, indicating altered mitochondrial dynamics. Wang *et al.* reported that treatment with resveratrol led to a significant reduction in the number of senescent yeast cells with fragmented mitochondria. This indicates that resveratrol's anti-aging effects possibly occur via modulating the expression of genes associated with mitochondrial dynamics during RLS.¹³⁰

Psoralea corylifolia

P. corylifolia is a medicinal plant widely used in the traditional medicine systems in India and China. Wang *et al.* showed that the ethanol extract of *P. corylifolia* significantly extended the RLS of yeast. In particular, the n-hexane fraction of the ethanol extract of *P. corylifolia* increased the yeast lifespan by 20%. Interestingly, the n-hexane extract of *P. corylifolia* extended the mean lifespan of the *sir2Δfob1Δ* double mutant strain, indicating that the n-hexane fraction prolongs the RLS in a Sir2-independent pathway. Treatment with *P. corylifolia* did not extend the RLS of the *tor1Δ* mutant, suggesting that Tor1 plays a major role in the extension of RLS by the n-hexane-soluble fraction *P. corylifolia*.

Furthermore, it was reported that, Corylin and neobavaisoflavone are the active compounds in *P. corylifolia* that significantly increased the viability and extended the RLS of yeast. In particular, corylin was found to be more effective in enhancing the yeast RLS compared to neobavaisoflavone. It was also shown that corylin treatment promoted RLS of the *sir2Δfob1Δ* mutant strain but failed to prolong the RLS of the *tor1Δ* mutant, suggesting that corylin exerts life span-extending effects in a Tor1-dependent pathway. Fascinatingly, under CR conditions, corylin could not extend the RLS. In addition, corylin treatment did not significantly influence the CLS of yeast. Gtr1 in *S. cerevisiae* encodes a highly conserved GTPase that is necessary for TORC1 activation and amino acid sensing. The G protein complex Gtr1/Gtr2 activates Tor1 in *S. cerevisiae* in response to signals from amino acids.¹⁴⁹ Furthermore, it was also suggested from docking studies that corylin prolongs the yeast RLS by blocking Gtr1 activation.¹³²

Previous studies by Lee MB *et al* also demonstrated that green tea extract and berberine could strongly shorten the yeast life span, whereas *Pterocarpus marsupium* extract and other mixtures containing *P. marsupium* significantly extended the yeast life span.¹³³ In another study, two sesquiterpene glucosides isolated from the Shenzhou honey peach fruit were also able to extend the RLS of K6001 yeast. Treatment with sesquiterpene glucosides increased the survival rate of yeast under oxidative stress. Besides, treatment with sesquiterpene glucosides could not affect the RLSs of SOD mutant yeast strains with a K6001 background, indicating that the anti-oxidative stress response performs important roles in anti-aging effects of sesquiterpene glucosides.¹²³

Natural products/plant extracts vs. both CLS & RLS

Some natural products have also been demonstrated to extend both RLS and CLS in yeast model. These natural products include curcumin (a diarylheptanoid),¹⁵⁰ Cucurbitacin B (a triterpenoid),¹³⁶ Gentirigeoside B (a dammar-type triterpenoid glycoside),¹⁵¹ Gentiopicroside (a secoiridoid glycoside),¹⁵² and inkosterone (a phytoecdysteroid).¹⁵³ Table 3 lists the natural compounds, their concentrations, phytochemical class, type of growth medium used for aging experiments, and their anti-aging mechanisms in different *S. cerevisiae* strain backgrounds.

Table 3. List of Natural products extending both CLS & RLS.

Name	Chemical Class	Dose	Yeast Strain	Yeast Growth Medium	Anti-Aging Mechanism	Ref.
Curcumin	Diarylheptanoid	200 & 300 µM	BY4741	SD	<ul style="list-style-type: none">Increased oxidative stress and resulting hormetic effects	150
Cucurbitacin B	Triterpenoid	0.1, 0.3, 1 µM	K6001	YPGal	<ul style="list-style-type: none">↑ ATG32 mRNA levels↓ ROS and MDA↑ SOD activity↑ SOD12 and SOD2 mRNA levels through the regulation of expression of <i>UTH1</i> as well as <i>SKN7</i>.	136
Gentirigeoside B	Dammaren-type triterpenoid glycoside	1, 3, and 10 µM	K6001	SD	<ul style="list-style-type: none">↑ Enzymatic activities of SOD, CAT, Gpx↓ ROS and MDA↓ SCH9 mRNA and ↑ mRNA levels of RIM15 and Msn2	151
Gentiopicroside	secoiridoid glycoside	1, 3, and 10 µM	K6001 and YOM36	SCM+ 2%glucose+ 2% peptone+1% yeast extract and SD	<ul style="list-style-type: none">↑ ATG32 mRNA levels↑ Activity of SOD, CAT, Gpx↓ ROS and MDA	152
Inokosterone	Phytoecdysone	0.1, 0.3, 1, 3, and 10 µM	K6001 and YOM36	YPGal and SD	<ul style="list-style-type: none">↑ Sod↓ ROS and MDA levels↑ autophagy (especially mitophagy)	153

YPD (1% yeast extract, 2% peptone, 2% dextrose); YPGal (1% yeast extract, 2% peptone, 2% Galactose); YPGly (1% yeast extract, 2% peptone, 3% Galactose); SCM (synthetic complete medium). SD (Synthetic defined) medium. Symbols '+' and '-' indicate up-regulation/increase and down-regulation/decrease, respectively.

Curcumin

Curcumin is a biologically active yellow-colored carotenoid compound with potent anti-oxidant and anti-aging properties. Previous studies investigated the replicative and chronological life span-extending effects of curcumin using yeast. It was demonstrated that curcumin significantly increased oxidative stress and enhanced both replicative and chronological life spans of yeast mutants that lacked antioxidant genes (*SOD1* and *SOD2*) and DNA damage repair gene *RAD52*. Overall, it can be suggested that curcumin exerts anti-aging hormetic effects in yeast.¹⁵⁰

Gentirigeoside B and gentiopicroside

Gentirigeoside B is a triterpenoid glycoside isolated from the Chinese traditional medicinal plant *Gentiana rigescens* Franch. Xiang, L., *et al.* reported that gentirigeoside B significantly extended both the replicative and chronological lifespans of yeast. It was also demonstrated that treatment with gentirigeoside B augmented the activity of antioxidant enzymes (including superoxide dismutase, catalase, and glutathione peroxidase) and reduced oxidative stress markers (ROS and MDA), thereby preventing oxidative stress-induced reduction in the viability of yeast cells. Gentirigeoside-B treated cells also showed downregulation of Sch9 and activation of Rim15 and Msn2 proteins. This indicates that the anti-aging potential of gentirigeoside B is due to its ability to inhibit the TORC1/Sch9/Rim15/Msn signaling. However, gentirigeoside B could not enhance the life span of yeast mutant lacking antioxidant genes (*sod1Δ*, *sod2Δ*, *cat1Δ*, and *gpxΔ*) and age-related genes (*skn7Δ* and *uth1Δ*). Therefore, Xiang, L., *et al.* suggested that though treatment with gentirigeoside B might have longevity-promoting effects in humans, the effect may not be effective in those with mutations in endogenous antioxidant enzyme genes.¹⁵¹

In another study, gentiopicroside, a secoiridoid glycoside that was also isolated from *G. rigescens* Franch was reported to extend both the RLS and the CLS of yeast. Gentiopicroside was shown to induce ATG32 gene expression, but could not prolong the RLS and CLS of yeast mutants deficient in ATG32 gene. It was also reported that gentiopicroside enhanced the yeast survival rate under oxidative stress condition by augmenting the activities of enzymatic antioxidants and diminishing the accumulation of ROS and lipid peroxidation. However, gentiopicroside could not affect the RLSs of *sod1Δ*, *sod2Δ*, *uth1Δ*, and *skn7Δ*. Overall, it can be suggested that gentiopicroside's anti-aging effects are attributed to its ability to ameliorate autophagy and antioxidative stress response.¹⁵²

Inokosterone

A recent study,⁵⁸ isolated a compound, inokosterone from *G. rigescens* Franch and demonstrated that inokosterone can extend both the chronological and replicative life spans. The inokosterone was shown to enhance the survival rate of yeast cells by ameliorating the levels of antioxidant enzymes (e.g., SOD) and preventing accumulation of oxidative stress markers (e.g., ROS and MDA levels). Further, inokosterone could alleviate the autophagy (especially mitophagy) in yeast cells. Likewise, the same study also demonstrated that treatment with inokosterone decreased oxidative stress and enhanced autophagy in mammalian cell lines. Therefore, it can be suggested that inokosterone's anti-aging effects are mediated through the activation of antioxidant stress response and mitophagy.¹⁵³

Emerging trends and future directions

An exponential interest in the pursuit for youthful, vital, and quality of human life have become the key driving forces in the development of novel scientific and technological advancements in the anti-aging field. Recent key developments in anti-aging research include nanocapsulation, nutrigenomics, stem cell therapy, *senescent therapy*, as well as the application of artificial intelligence (AI). These innovations are useful for forecasting the potential of different anti-aging treatments and to develop personalized anti-aging strategies. *Nanocapsulation* of anti-aging compounds ensure their sustainable release at target site improving the therapeutic effectiveness. The development of personalized anti-aging nanoformulations might enhance treatment efficacy with minimal side effects.^{154,155} *Nutrigenomics* is an emerging field that explores how nutrients and dietary factors influence cellular processes. This research focuses on how these factors can modulate age-related gene expression, reduce the risk of age-related diseases, and improve overall quality of life. Understanding gene-diet interactions may allow for the development of precise anti-aging nutritional strategies to promote health and longevity.¹⁵⁶ *Stem cell therapy*, particularly, the use of mesenchymal stem cells that can differentiate into skin cells, make them potentially restore skin elasticity and combat skin-aging.¹⁵⁷ *Senotherapy*: There has been a growing interest in the screening, identification, evaluation, and development of potent senotherapeutics including senolytics that selectively kill senescent cells and senostatics/senomorphics that reduce the senescent associated pro-inflammatory phenotype, thereby improving healthspan and potentially reducing the prevalence of chronic conditions.¹⁵⁸ *Artificial Intelligence (AI)*: The revolutionary development of AI algorithms could help in predicting different age-related biomarkers and the progression of age-linked diseases, such as cancer, cardiovascular diseases, neurodegenerative diseases, diabetes, etc.¹⁵⁹ AI's ability to predict diseases related biomarkers offers hope for developing targeted anti-aging therapies and managing the disease risk associated with an aging population.

Conclusions

Aging is a significant risk factor for the emergence of several chronic human diseases. In order to reduce the pathophysiology of diseases related to aging and to increase the active lifetime of people, aging research is primarily concerned with the identification of new anti-aging therapies. Budding yeast *S. cerevisiae* has been used as a valuable model to evaluate the anti-aging properties of phytochemicals as well as synthetic compounds. Several studies demonstrated that plant extracts/phytochemicals can increase longevity via regulation of various pathways including the TORC1/Sch9/Rim15/Msn signaling pathway, RAS-AC-PKA pathway, Sir2-dependent pathway, NAD⁺-salvage pathway, Uth1/TOR signaling, and antioxidant stress response pathway as well as autophagy. Notably, some natural products exert their anti-aging potential by enhancing the hormetic response in aging yeast cells.

While many of these studies reported enhancing the yeast cell's oxidative stress resistance, a few studies have also documented the pro-oxidant effects of various antioxidants, suggesting dose-dependent effects on life span. For example, in the K6001 yeast strain of *S. cerevisiae*, treatment with alpha-tocopherol and coenzyme Q10 enhanced oxidative stress and shortened RLS, showing the potential pro-oxidant effects of antioxidants that may be dose-dependent.¹⁶⁰ Therefore, to maximize the therapeutic benefits of antioxidants, it is necessary to evaluate their dose-dependent effects as well as potential pro-oxidant actions. Mounting evidence from anti-aging research using yeast models is invaluable in exploring the CR mimetic effects of natural products like artesunate.⁸⁷ The discovery of novel plant-derived chemicals with anti-aging activities opens up new opportunities for developing leading medications for the treatment of age-related disorders.

Several factors influence yeast survival during chronological aging, such as the concentration of the primary carbon source (like glucose), different types of other carbon sources (e.g., ethanol and acetic acid), the composition of amino acids in the growth medium, and the pH of the aging culture medium can affect the survival of yeast cell during chronological aging. More than 1000 genes are linked to variations in CLS in *S. cerevisiae*, highlighting significant role of genetic material in understanding the fundamental molecular and cellular processes controlling life span in eukaryotes. Most of the anti-aging research studies reviewed here focus on gene deletion mutant strains, which are associated with some drawbacks.¹⁶¹ For instance, gene deletion mutant strains also harbor a secondary mutation (e.g., auxotrophies lacking additional genes like URA or TRP), resulting in heterogenous populations in over 50 % of the strains.¹⁶² This heterogeneity can lead to the misinterpretations of genotype and phenotype associations. Furthermore, all gene deletion mutant strains are typically derived from few laboratory strains, primarily the BY strain. This By strain exhibits extreme phenotypic traits that may not accurately represent the natural diversity of the *S. cerevisiae* species.¹⁶³

In conclusion, aging research using budding yeast as a model organism has yielded valuable insights into the anti-aging properties of various compounds, and the identification of specific pathways and mechanisms involved contributes to the development of potential anti-aging therapies for improving health span and longevity in humans. Continued research into plant extracts and natural compounds may lead to the identification of promising candidates for fighting age-related disorders in the future.

Data availability

No data are associated with this article.

Acknowledgements

Phaniendra Alugoju thanks to C2F (Secondary Century Fund) Postdoctoral Fellowship, Chulalongkorn University, Bangkok 10330, Thailand. All figures were created with [BioRender.com](https://www.biorender.com).

References

- Hou Y, Dan X, Babbar M, et al.: **Ageing as a risk factor for neurodegenerative disease.** *Nat Rev Neurol.* 2019 Oct; **15**(10): 565–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Costantino S, Paneni F, Cosentino F: **Ageing, metabolism and cardiovascular disease.** *J Physiol.* 2016 Apr 15; **594**(8): 2061–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Blagosklonny MV: **Prospective treatment of age-related diseases by slowing down aging.** *Am J Pathol.* 2012 Oct; **181**(4): 1142–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- López-Otín C, Blasco MA, Partridge L, et al.: **Hallmarks of aging: An expanding universe.** *Cell.* 2023; **186**(2): 243–78.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Schmauck-Medina T, Molière A, Lautrup S, et al.: **New hallmarks of ageing: a 2022 Copenhagen ageing meeting summary.** *Aging (Albany NY).* 2022 Aug 29; **14**(16): 6829–39.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Liu JK: **Antiaging agents: safe interventions to slow aging and healthy life span extension.** *Nat Prod Bioprospect.* 2022 May 9; **12**(1): 18.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

7. Guo J, Huang X, Dou L, *et al.*: **Aging and aging-related diseases: from molecular mechanisms to interventions and treatments.** *Signal Transduct Target Ther.* 2022 Dec 16; **7**(1): 391.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
8. Le Couteur DG, Solon-Biet SM, Parker BL, *et al.*: **Nutritional reprogramming of mouse liver proteome is dampened by metformin, resveratrol, and rapamycin.** *Cell Metab.* 2021 Dec 7; **33**(12): 2367–79.e4.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Li Y, Tian X, Luo J, *et al.*: **Molecular mechanisms of aging and anti-aging strategies.** *Cell Commun Signal.* 2024 May 24; **22**(1): 285.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
10. Borchardt JK: **The Beginnings of drug therapy: ancient mesopotamian medicine.** *Drug News Perspect.* 2002; **15**(3): 187–192.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Schmidt R: **The Pharmacology of Chinese Herbs, Kee Chang Huang.** CRC Press, Boca Raton. Florida. 1993; 1994(01/01): 10.
12. Dev S: **Ancient-modern concordance in ayurvedic plants: Some examples.** *Environ Health Perspect.* 1999; **107**(10): 783–789.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. Farnsworth NR, Akerele O, Bingle AS, *et al.*: **Medicinal plants in therapy.** *Bull World Health Organ.* 1985; **63**(6): 965–981.
[PubMed Abstract](#)
14. Fabricant DS, Farnsworth NR: **The value of plants used in traditional medicine for drug discovery.** *Environ Health Perspect.* 2001; **109** Suppl 1(SUPPL 1): 69–75.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Buss AD, Cox B, Waigh RD: **Natural Products as Leads for New Pharmaceuticals.** Burger's Medicinal Chemistry and Drug Discovery. pp. 847–900.
16. Tu Y: **The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine.** *Nat Med.* 2011; **17**(10): 1217–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
17. Kingston DG: **Taxol and its analogs.** *Anticancer Agents from Natural Products.* 2005; pp. 89–122.
[Publisher Full Text](#)
18. Guérítte F, Fahy J: **The vinca alkaloids.** *Anticancer Agents from Natural Products.* 2005; pp. 123–36.
[Publisher Full Text](#)
19. Kapoor L: **CRC handbook of Ayurvedic medicinal plants.** CRC Press; 2018.
[Publisher Full Text](#)
20. Cragg GM, Newman DJ: **Natural products: A continuing source of novel drug leads.** *Biochim Biophys Acta.* 2013; **1830**(6): 3670–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. Butler MS: **Natural products to drugs: natural product-derived compounds in clinical trials.** *Nat Prod Rep.* 2008; **25**(3): 475–516.
[PubMed Abstract](#) | [Publisher Full Text](#)
22. Nurmikko TJ, Serpell MG, Hoggart B, *et al.*: **Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial.** *Pain.* 2007; **133**(1-3): 210–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. Johnson JR, Burnell-Nugent M, Lossignol D, *et al.*: **Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain.** *J Pain Symptom Manage.* 2010; **39**(2): 167–79.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Mori A, Lehmann S, O'Kelly J, *et al.*: **Capsaicin, a component of red peppers, inhibits the growth of androgen-independent, p53 mutant prostate cancer cells.** *Cancer Res.* 2006; **66**(6): 3222–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Moskalev A, Guvatova Z, Lopes IA, *et al.*: **Targeting aging mechanisms: pharmacological perspectives.** *Trends Endocrinol Metab.* 2022 Apr; **33**(4): 266–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
26. Rattan SI: **Anti-ageing strategies: prevention or therapy? Showing ageing from within.** *EMBO Rep.* 2005 Jul; **6** Spec No(Suppl 1): S25–9.
[PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#)
27. Bakula D, Ablasser A, Aguzzi A, *et al.*: **Latest advances in aging research and drug discovery.** *Aging (Albany NY).* 2019 Nov 21; **11**(22): 9971–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Taormina G, Ferrante F, Vieni S, *et al.*: **Longevity: Lesson from Model Organisms.** *Genes (Basel).* 2019 Jul 9; **10**(7).
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Zimmermann A, Hofer S, Pendl T, *et al.*: **Yeast as a tool to identify anti-aging compounds.** *FEMS Yeast Res.* 2018 Sep 1; **18**(6).
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. Kirchweber B, Zwirchmayr J, Grienke U, *et al.*: **The role of *Caenorhabditis elegans* in the discovery of natural products for healthy aging.** *Nat Prod Rep.* 2023 Aug 16; **40**: 1849, 1873.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Yanni S, Muhammad Eka P, Roni M, *et al.*: **The Budding Yeast *Saccharomyces cerevisiae* as a Valuable Model Organism for Investigating Anti-Aging Compounds.** In: Thaita Peixoto B, Luiz Carlos B, editors. *Saccharomyces*. Rijeka: IntechOpen; 2021. Ch. 6.
32. Goffeau A, Barrell BG, Bussey H, *et al.*: **Life with 6000 genes.** *Science.* 1996 Oct 25; **274**(5287): 546.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Mortimer RK, Johnston JR: **Life span of individual yeast cells.** *Nature.* 1959 Jun 20; **183**(4677): 1751–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Longo VD, Shadel GS, Kaerberlein M, *et al.*: **Replicative and chronological aging in *Saccharomyces cerevisiae*.** *Cell Metab.* 2012 Jul 3; **16**(1): 18–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
35. Kaerberlein M: **Lessons on longevity from budding yeast.** *Nature.* 2010 Mar 25; **464**(7288): 513–9.
[PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#)
36. Ganley AR, Ide S, Saka K, *et al.*: **The effect of replication initiation on gene amplification in the rDNA and its relationship to aging.** *Mol Cell.* 2009 Sep 11; **35**(5): 683–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Erjavec N, Nyström T: **Sir2p-dependent protein segregation gives rise to a superior reactive oxygen species management in the progeny of *Saccharomyces cerevisiae*.** *Proc Natl Acad Sci U S A.* 2007 Jun 26; **104**(26): 10877–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
38. Aguilaniu H, Gustafsson L, Rigoulet M, *et al.*: **Asymmetric inheritance of oxidatively damaged proteins during cytokinesis.** *Science.* 2003 Mar 14; **299**(5613): 1751–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Lai CY, Jaruga E, Borghouts C, *et al.*: **A mutation in the ATP2 gene abrogates the age asymmetry between mother and daughter cells of the yeast *Saccharomyces cerevisiae*.** *Genetics.* 2002 Sep; **162**(1): 73–87.
[PubMed Abstract](#) | [Free Full Text](#)
40. Borghouts C, Benguria A, Wawryn J, *et al.*: **Rtg2 Protein Links Metabolism and Genome Stability in Yeast Longevity.** *Genetics.* 2004; **166**(2): 765–777.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Bitto A, Wang AM, Bennett CF, *et al.*: **Biochemical Genetic Pathways that Modulate Aging in Multiple Species.** Cold Spring Harb Perspect Med. 2015 Nov 2; **5**(11). Epub 20151102. eng.
[PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#)
42. Allen C, Büttner S, Aragon AD, *et al.*: **Isolation of quiescent and nonquiescent cells from yeast stationary-phase cultures.** *J Cell Biol.* 2006 Jul 3; **174**(1): 89–100.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. Longo VD, Fabrizio P: **Chronological aging in *Saccharomyces cerevisiae*.** *Subcell Biochem.* 2012; **57**: 101–21.
[PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#)
44. Galdieri L, Mehrotra S, Yu S, Vancura A: **Transcriptional regulation in yeast during diauxic shift and stationary phase.** *Omic.* 2010 Dec; **14**(6): 629–38.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. Orlandi I, Ronzulli R, Casatta N, *et al.*: **Ethanol and Acetate Acting as Carbon/Energy Sources Negatively Affect Yeast Chronological Aging.** *Oxid Med Cell Longev.* 2013; **2013**(1): 802870.
[Publisher Full Text](#)
46. Burtner CR, Murakami CJ, Kennedy BK, *et al.*: **A molecular mechanism of chronological aging in yeast.** *Cell Cycle.* 2009 Apr 15; **8**(8): 1256–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
47. Fabrizio P, Liou LL, Moy VN, *et al.*: **SOD2 functions downstream of Sch9 to extend longevity in yeast.** *Genetics.* 2003 Jan; **163**(1): 35–46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
48. Longo VD, Gralla EB, Valentine JS: **Superoxide dismutase activity is essential for stationary phase survival in *Saccharomyces cerevisiae*. Mitochondrial production of toxic oxygen species in vivo.** *J Biol Chem.* 1996 May 24; **271**(21): 12275–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
49. Wawryn J, Krzepilko A, Myszk A, *et al.*: **Deficiency in superoxide dismutases shortens life span of yeast cells.** *Acta Biochim Pol.* 1999; **46**(2): 249–53.
[PubMed Abstract](#) | [Publisher Full Text](#)

50. Santos J, Leão C, Sousa MJ: **Growth culture conditions and nutrient signaling modulating yeast chronological longevity.** *Oxid Med Cell Longev*. 2012; **2012**: 680304. Epub 20120809. eng. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
51. Kaerberlein M, Powers RW 3rd, Steffen KK, *et al.*: **Regulation of yeast replicative life span by TOR and Sch9 in response to nutrients.** *Science*. 2005 Nov 18; **310**(5751): 1193–6. [PubMed Abstract](#) | [Publisher Full Text](#)
52. Powers RW 3rd, Kaerberlein M, Caldwell SD, *et al.*: **Extension of chronological life span in yeast by decreased TOR pathway signaling.** *Genes Dev*. 2006 Jan 15; **20**(2): 174–84. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
53. Bisschops MMM, Zwartjens P, Keuter SGF, *et al.*: **To divide or not to divide: A key role of Rim15 in calorie-restricted yeast cultures.** *Biochim Biophys Acta, Mol Cell Res*. 2014; **1843**(5): 1020–30. [Publisher Full Text](#)
54. Gyöngyösi N, Szőke A, Ella K, *et al.*: **The small G protein RAS2 is involved in the metabolic compensation of the circadian clock in the circadian model *Neurospora crassa*.** *J Biol Chem*. 2017 Sep 8; **292**(36): 14929–39. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
55. Pylayeva-Gupta Y, Grabocka E, Bar-Sagi D: **RAS oncogenes: weaving a tumorigenic web.** *Nat Rev Cancer*. 2011; **11**(11): 761–74. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
56. Kataoka T, Powers S, McGill C, *et al.*: **Genetic analysis of yeast RAS1 and RAS2 genes.** *Cell*. 1984 Jun; **37**(2): 437–45. [PubMed Abstract](#) | [Publisher Full Text](#)
57. Longo VD: **Mutations in signal transduction proteins increase stress resistance and longevity in yeast, nematodes, fruit flies, and mammalian neuronal cells.** *Neurobiol Aging*. 1999; **20**(5): 479–86. [PubMed Abstract](#) | [Publisher Full Text](#)
58. Kraakman L, Lemaire K, Ma P, *et al.*: **A *Saccharomyces cerevisiae* G-protein coupled receptor, Gpr1, is specifically required for glucose activation of the cAMP pathway during the transition to growth on glucose.** *Mol Microbiol*. 1991; **5**(6): 1301–7. [PubMed Abstract](#) | [Publisher Full Text](#)
59. Thevelein JM: **Fermentable sugars and intracellular acidification as specific activators of the RAS-adenylate cyclase signalling pathway in yeast: the relationship to nutrient-induced cell cycle control.** *Mol Microbiol*. 1991; **5**(6): 1301–7. [PubMed Abstract](#) | [Publisher Full Text](#)
60. Fabrizio P, Pozza F, Pletcher SD, *et al.*: **Regulation of Longevity and Stress Resistance by Sch9 in Yeast.** *Science*. 2001; **292**(5515): 288–90. [PubMed Abstract](#) | [Publisher Full Text](#)
61. Matsumoto K, Uno I, Oshima Y, *et al.*: **Isolation and characterization of yeast mutants deficient in adenylate cyclase and cAMP-dependent protein kinase.** *Proc Natl Acad Sci U S A*. 1982; **79**(7): 2355–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
62. Zaman S, Lippman SI, Schnepfer L, *et al.*: **Glucose regulates transcription in yeast through a network of signaling pathways.** *Mol Syst Biol*. 2009; **5**: 245. Epub 20090217. eng. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
63. Thevelein JM, de Winder JH: **Novel sensing mechanisms and targets for the cAMP-protein kinase A pathway in the yeast *Saccharomyces cerevisiae*.** *Mol Microbiol*. 1999 Sep; **33**(5): 904–18. [PubMed Abstract](#) | [Publisher Full Text](#)
64. Wei M, Fabrizio P, Hu J, *et al.*: **Life span extension by calorie restriction depends on Rim15 and transcription factors downstream of Ras/PKA, Tor, and Sch9.** *PLoS Genet*. 2008 Jan; **4**(1): e13. Epub 20071213. eng. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. Migliaccio E, Giorgio M, Mele S, *et al.*: **The p66shc adaptor protein controls oxidative stress response and life span in mammals.** *Nature*. 1999 Nov 18; **402**(6759): 309–13. [PubMed Abstract](#) | [Publisher Full Text](#)
66. Yan L, Vatner DE, O'Connor JP, *et al.*: **Type 5 adenylyl cyclase disruption increases longevity and protects against stress.** *Cell*. 2007 Jul 27; **130**(2): 247–58. [PubMed Abstract](#) | [Publisher Full Text](#)
67. Søberg K, Skålhegg BS: **The Molecular Basis for Specificity at the Level of the Protein Kinase a Catalytic Subunit.** *Front Endocrinol (Lausanne)*. 2018 2018-September-12; **9**. English. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
68. Enns LC, Morton JF, Treuting PR, *et al.*: **Disruption of protein kinase A in mice enhances healthy aging.** *PLoS One*. 2009 Jun 18; **4**(6): e5963. Epub 20090618. eng. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
69. González A, Hall MN: **Nutrient sensing and TOR signaling in yeast and mammals.** *Embo J*. 2017 Feb 15; **36**(4): 397–408. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. Heitman J, Movva NR, Hall MN: **Targets for cell cycle arrest by the immunosuppressant rapamycin in yeast.** *Science*. 1991 Aug 23; **253**(5022): 905–9. [PubMed Abstract](#) | [Publisher Full Text](#)
71. Kamada Y, Umeda C, Mukai Y, *et al.*: **Structure-based engineering of Tor complexes reveals that two types of yeast TORC1 produce distinct phenotypes.** *J Cell Sci*. 2024 Feb 15; **137**(4). Epub 20240228. eng. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
72. Brown EJ, Albers MW, Shin TB, *et al.*: **A mammalian protein targeted by G1-arresting rapamycin-receptor complex.** *Nature*. 1994 Jun 30; **369**(6483): 756–8. [PubMed Abstract](#) | [Publisher Full Text](#)
73. Sabers CJ, Martin MM, Brunn GJ, *et al.*: **Isolation of a protein target of the FKBP12-rapamycin complex in mammalian cells.** *J Biol Chem*. 1995 Jan 13; **270**(2): 815–22. [PubMed Abstract](#) | [Publisher Full Text](#)
74. Loewith R, Jacinto E, Wullschlegel S, *et al.*: **Two TOR complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control.** *Mol Cell*. 2002 Sep; **10**(3): 457–68. [PubMed Abstract](#) | [Publisher Full Text](#)
75. Urban J, Souillard A, Huber A, *et al.*: **Sch9 is a major target of TORC1 in *Saccharomyces cerevisiae*.** *Mol Cell*. 2007 Jun 8; **26**(5): 663–74. [PubMed Abstract](#) | [Publisher Full Text](#)
76. Roelants FM, Torrance PD, Bezman N, *et al.*: **Pkh1 and Pkh2 differentially phosphorylate and activate Ypk1 and Ykr2 and define protein kinase modules required for maintenance of cell wall integrity.** *Mol Biol Cell*. 2002 Sep; **13**(9): 3005–28. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
77. Voordeckers K, Kimpe M, Haesendonckx S, *et al.*: **Yeast 3-phosphoinositide-dependent protein kinase-1 (PDK1) orthologs Pkh1-3 differentially regulate phosphorylation of protein kinase A (PKA) and the protein kinase B (PKB)/S6K ortholog Sch9.** *J Biol Chem*. 2011 Jun 24; **286**(25): 22017–27. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
78. Hsu J-W, Chen K-J, Lee F-JS: **Snf1/AMP-activated protein kinase activates Arf3p to promote invasive yeast growth via a non-canonical GEF domain.** *Nat Commun*. 2015; **6**(1): 7840. [Publisher Full Text](#)
79. Kaerberlein M, Powers RW, Steffen KK, *et al.*: **Regulation of Yeast Replicative Life Span by TOR and Sch9 in Response to Nutrients.** *Science*. 2005; **310**(5751): 1193–6. [Publisher Full Text](#)
80. Wei M, Fabrizio P, Madia F, *et al.*: **Tor1/Sch9-Regulated Carbon Source Substitution Is as Effective as Calorie Restriction in Life Span Extension.** *PLoS Genet*. 2009; **5**(5): e1000467. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
81. Kaerberlein M: **Lessons on longevity from budding yeast.** *Nature*. 2010; **464**: 513–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
82. Fontana L, Partridge L, Longo VD: **Extending healthy life span--from yeast to humans.** *Science*. 2010 Apr 16; **328**(5976): 321–6. [PubMed Abstract](#) | [Free Full Text](#)
83. Wang Y, Cao X, Ma J, *et al.*: **Unveiling the Longevity Potential of Natural Phytochemicals: A Comprehensive Review of Active Ingredients in Dietary Plants and Herbs.** *J Agric Food Chem*. 2024 Nov 13; **72**(45): 24908–27. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
84. Li Z, Chen L, Qu L, *et al.*: **Potential implications of natural compounds on aging and metabolic regulation.** *Ageing Res Rev*. 2024; **101**: 102475. [PubMed Abstract](#) | [Publisher Full Text](#)
85. SJ S, Veerabhadrapa B, Subramaniyan S, *et al.*: **Astaxanthin enhances the longevity of *Saccharomyces cerevisiae* by decreasing oxidative stress and apoptosis.** *FEMS Yeast Res*. 2019 Jan 1; **19**(1). eng. [PubMed Abstract](#) | [Publisher Full Text](#)
86. Sudharshan SJ, Dyavaiah M: **Astaxanthin protects oxidative stress mediated DNA damage and enhances longevity in *Saccharomyces cerevisiae*.** *Biogerontology*. 2021 Feb; **22**(1): 81–100. [PubMed Abstract](#) | [Publisher Full Text](#)
87. Wang D, Wu M, Li S, *et al.*: **Artemisinin mimics calorie restriction to extend yeast lifespan via a dual-phase mode: a conclusion drawn from global transcriptome profiling.** *Sci China Life Sci*. 2015 May; **58**(5): 451–65. [PubMed Abstract](#) | [Publisher Full Text](#)
88. Sudharshan SJ, Krishna Narayanan A, *et al.*: **Betulinic acid mitigates oxidative stress-mediated apoptosis and enhances longevity in**

- the yeast *Saccharomyces cerevisiae* model.** *Free Radic Res.* 2022 Nov-Dec; **56**(11-12): 699–712.
[PubMed Abstract](#) | [Publisher Full Text](#)
89. Guo C, Zhang H, Guan X, *et al.*: **The Anti-Aging Potential of Neohesperidin and Its Synergistic Effects with Other Citrus Flavonoids in Extending Chronological Lifespan of *Saccharomyces Cerevisiae* BY4742.** *Molecules.* 2019 Nov 13; **24**(22). Epub 20191113. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 90. Tungmunthithum D, Abid M, Elamrani A, *et al.*: **Almond Skin Extracts and Chlorogenic Acid Delay Chronological Aging and Enhanced Oxidative Stress Response in Yeast.** *Life (Basel).* 2020 May 28; **10**(6). Epub 20200528. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 91. Wang S, Qiao J, Jiang C, *et al.*: **Ginsenoside Rg1 Delays Chronological Aging in a Yeast Model via CDC19- and SDH2-Mediated Cellular Metabolism.** *Antioxidants (Basel).* 2023 Jan 28; **12**(2). Epub 20230128. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 92. Subramaniam S, Alugoju P, Sij S, *et al.*: **Magnolol protects *Saccharomyces cerevisiae* antioxidant-deficient mutants from oxidative stress and extends yeast chronological life span.** *FEMS Microbiol Lett.* 2019 Apr 1; **366**(8). eng.
[PubMed Abstract](#) | [Publisher Full Text](#)
 93. Palermo V, Falcone C, Calvani M, *et al.*: **Acetyl-L-carnitine protects yeast cells from apoptosis and aging and inhibits mitochondrial fission.** *Aging Cell.* 2010 Aug; **9**(4): 570–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 94. Sun K, Xiang L, Ishihara S, *et al.*: **Anti-aging effects of hesperidin on *Saccharomyces cerevisiae* via inhibition of reactive oxygen species and UTH1 gene expression.** *Biosci Biotechnol Biochem.* 2012; **76**(4): 640–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 95. Kadlecová A, Maková B, Artal-Sanz M, *et al.*: **The plant hormone kinetin in disease therapy and healthy aging.** *Ageing Res Rev.* 2019 Nov; **55**: 100958. Epub 20190831. eng.
[PubMed Abstract](#) | [Publisher Full Text](#)
 96. Orlicka-Płocka M, Fedoruk-Wysomirska A, Gurda-Woźna D, *et al.*: **Implications of Oxidative Stress in Glioblastoma Multiforme Following Treatment with Purine Derivatives.** *Antioxidants (Basel).* 2021 Jun 12; **10**(6). Epub 20210612. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 97. Pawelczak P, Fedoruk-Wysomirska A, Wyszko E: **Antianging Effect of 4-N-Furfurylcytosine in Yeast Model Manifests through Enhancement of Mitochondrial Activity and ROS Reduction.** *Antioxidants (Basel).* 2022 Apr 26; **11**(5). Epub 20220426. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 98. Kavitate D, Veerabhadrapa B, Sudharshan SJ, *et al.*: **Oxidative stress alleviating potential of galactan exopolysaccharide from *Weissella confusa* KR780676 in yeast model system.** *Sci Rep.* 2022 Jan 20; **12**(1): 1089. Epub 20220120. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 99. Wu Z, Song L, Liu SQ, Huang D: **Independent and additive effects of glutamic acid and methionine on yeast longevity.** *PLoS One.* 2013; **8**(11): e79319. Epub 20131107. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 100. Arlia-Ciommo A, Leonov A, Mohammad K, *et al.*: **Mechanisms through which lithocholic acid delays yeast chronological aging under caloric restriction conditions.** *Oncotarget.* 2018 Oct 9; **9**(79): 34945–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 101. Burstain MT, Kyryakov P, Beach A, *et al.*: **Lithocholic acid extends longevity of chronologically aging yeast only if added at certain critical periods of their lifespan.** *Cell Cycle.* 2012 Sep 15; **11**(18): 3443–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 102. Beach A, Richard VR, Bourque S, *et al.*: **Lithocholic bile acid accumulated in yeast mitochondria orchestrates a development of an anti-aging cellular pattern by causing age-related changes in cellular proteome.** *Cell Cycle.* 2015; **14**(11): 1643–56.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 103. Leonov A, Arlia-Ciommo A, Bourque SD, *et al.*: **Specific changes in mitochondrial lipidome alter mitochondrial proteome and increase the geroprotective efficiency of lithocholic acid in chronologically aging yeast.** *Oncotarget.* 2017 May 9; **8**(19): 30672–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 104. Xu P, Chen Q, Chen X, *et al.*: **Morusin and mulberrin extend the lifespans of yeast and *C. elegans* via suppressing nutrient-sensing pathways.** *Geroscience.* 2023 Apr; **45**(2): 949–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 105. Urban J, Souillard A, Huber A, *et al.*: **Sch9 Is a Major Target of TORC1 in *Saccharomyces cerevisiae*.** *Mol Cell.* 2007; **26**(5): 663–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
 106. Drozdova P, Lipaeva P, Rogozha T, *et al.*: **Overproduction of Sch9 leads to its aggregation and cell elongation in *Saccharomyces cerevisiae*.** *PLoS One.* 2018; **13**(3): e0193726.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 107. Mendes V, Vilaça R, de Freitas V, *et al.*: **Effect of myricetin, pyrogallol, and phloroglucinol on yeast resistance to oxidative stress.** *Oxid Med Cell Longev.* 2015; **2015**: 782504. Epub 20150427. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 108. Alugoju P, Janardhanashetty SS, Subaramanian S, *et al.*: **Quercetin Protects Yeast *Saccharomyces cerevisiae* pep4 Mutant from Oxidative and Apoptotic Stress and Extends Chronological Lifespan.** *Curr Microbiol.* 2018 May; **75**(5): 519–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
 109. Alugoju P, Periyasamy L, Dyavaiah M: **Quercetin enhances stress resistance in *Saccharomyces cerevisiae* tel1 mutant cells to different stressors.** *J Food Sci Technol.* 2018 Apr; **55**(4): 1455–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 110. Eisenberg T, Knauer H, Schauer A, *et al.*: **Induction of autophagy by spermidine promotes longevity.** *Nat Cell Biol.* 2009 Nov; **11**(11): 1305–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
 111. Wu Z, Song L, Liu SQ, *et al.*: **Tanshinones extend chronological lifespan in budding yeast *Saccharomyces cerevisiae*.** *Appl Microbiol Biotechnol.* 2014 Oct; **98**(20): 8617–28.
[PubMed Abstract](#) | [Publisher Full Text](#)
 112. Czachor J, Milek M, Galiniak S, *et al.*: **Coffee Extends Yeast Chronological Lifespan through Antioxidant Properties.** *Int J Mol Sci.* 2020 Dec 14; **21**(24). Epub 20201214. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 113. Hemagirri M, Sasidharan S: **In vitro antiaging activity of polyphenol rich *Polyalthia longifolia* (Annonaceae) leaf extract in *Saccharomyces cerevisiae* BY611 yeast cells.** *J Ethnopharmacol.* 2022; **290**: 115110.
[PubMed Abstract](#) | [Publisher Full Text](#)
 114. Hemagirri M, Sasidharan S: **Evaluation of In Situ Antiaging Activity in *Saccharomyces cerevisiae* BY611 Yeast Cells Treated with *Polyalthia longifolia* Leaf Methanolic Extract (PLME) Using Different Microscopic Approaches: A Morphology-Based Evaluation.** *Microsc Microanal.* 2022 Mar 9: 1–13. Epub ahead of print.
[PubMed Abstract](#) | [Publisher Full Text](#)
 115. Deng GF, Xu XR, Zhang Y, *et al.*: **Phenolic compounds and bioactivities of pigmented rice.** *Crit Rev Food Sci Nutr.* 2013; **53**(3): 296–306.
[PubMed Abstract](#) | [Publisher Full Text](#)
 116. Sunthongkun P, Palajai R, Somboon P, *et al.*: **Life-span extension by pigmented rice bran in the model yeast *Saccharomyces cerevisiae*.** *Sci Rep.* 2019 Dec 2; **9**(1): 18061. Epub 20191202. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 117. Tungmunthithum D, Drouet S, Hano C: **Validation of a High-Performance Liquid Chromatography with Photodiode Array Detection Method for the Separation and Quantification of Antioxidant and Skin Anti-Aging Flavonoids from *Nelumbo nucifera* Gaertn. Stamen Extract.** *Molecules.* 2022 Feb 7; **27**(3). Epub 20220207. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 118. Lutchman V, Dakik P, McAuley M, *et al.*: **Six plant extracts delay yeast chronological aging through different signaling pathways.** *Oncotarget.* 2016 Aug 9; **7**(32): 50845–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 119. Lutchman V, Medkour Y, Samson E, *et al.*: **Discovery of plant extracts that greatly delay yeast chronological aging and have different effects on longevity-defining cellular processes.** *Oncotarget.* 2016 Mar 29; **7**(13): 16542–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 120. Dakik P, McAuley M, Chancharoen M, *et al.*: **Pairwise combinations of chemical compounds that delay yeast chronological aging through different signaling pathways display synergistic effects on the extent of aging delay.** *Oncotarget.* 2019 Jan 8; **10**(3): 313–38.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 121. Medkour Y, Mohammad K, Arlia-Ciommo A, *et al.*: **Mechanisms by which PE21, an extract from the white willow *Salix alba*, delays chronological aging in budding yeast.** *Oncotarget.* 2019 Oct 8; **10**(56): 5780–816.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 122. Kwong MMY, Lee JW, Samian MR, *et al.*: **Identification of Tropical Plant Extracts That Extend Yeast Chronological Life Span.** *Cells.*

- 2021 Oct 11; 10(10). Epub 20211011. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
123. Wang Y, Lin Y, Xiang L, et al.: **Sesquiterpene glucosides from Shenzhou honey peach fruit showed the anti-aging activity in the evaluation system using yeasts.** *Biosci Biotechnol Biochem.* 2017 Aug; **81**(8): 1586–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
 124. Tungmunthum D, Drouet S, Hano C: **Flavonoids from Sacred Lotus Stamen Extract Slows Chronological Aging in Yeast Model by Reducing Oxidative Stress and Maintaining Cellular Metabolism.** *Cells.* 2022 Feb 9; **11**(4). Epub 20220209. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 125. Disasa D, Cheng L, Manzoor M, et al.: **Amarogentin from Gentiana rigescens Franch Exhibits Antiaging and Neuroprotective Effects through Antioxidative Stress.** *Oxid Med Cell Longev.* 2020; **2020**: 3184019. Epub 20200801. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 126. Cao X, Sun Y, Lin Y, et al.: **Antiaging of Cucurbitane Glycosides from Fruits of Momordica charantia L.** *Oxid Med Cell Longev.* 2018; **2018**: 1538632. Epub 20180325. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 127. Weng Y, Xiang L, Matsuura A, et al.: **Ganodermasides A and B, two novel anti-aging ergosterols from spores of a medicinal mushroom Ganoderma lucidum on yeast via UTH1 gene.** *Bioorg Med Chem.* 2010; **18**(3): 999–1002.
[PubMed Abstract](#) | [Publisher Full Text](#)
 128. Sun Y, Wang Y, Wang G, et al.: **A New Anti-Aging Lysophosphatidic Acid from Arabidopsis thaliana.** *Med Chem.* 2017; **13**(7): 641–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 129. Xiang L, Sun K, Lu J, et al.: **Anti-aging effects of phloridzin, an apple polyphenol, on yeast via the SOD and Sir2 genes.** *Biosci Biotechnol Biochem.* 2011; **75**(5): 854–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 130. Wang IH, Chen HY, Wang YH, et al.: **Resveratrol modulates mitochondria dynamics in replicative senescent yeast cells.** *PLoS One.* 2014; **9**(8): e104345. Epub 20140806. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 131. Lin Y, Sun Y, Weng Y, et al.: **Parishin from Gastrodia elata Extends the Lifespan of Yeast via Regulation of Sir2/Uth1/TOR Signaling Pathway.** *Oxid Med Cell Longev.* 2016; **2016**: 4074690. Epub 20160627. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 132. Wang TH, Tseng WC, Leu YL, et al.: **The flavonoid corylin exhibits lifespan extension properties in mouse.** *Nat Commun.* 2022 Mar 9; **13**(1): 1238. Epub 20220309. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 133. Lee MB, Kiflezghi MG, Tsuchiya M, et al.: **Pterocarpus marsupium extract extends replicative lifespan in budding yeast.** *Geroscience.* 2021 Oct; **43**(5): 2595–609.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 134. Cai Y, Fang X, He C, et al.: **Cucurbitacins: A Systematic Review of the Phytochemistry and Anticancer Activity.** *Am J Chin Med.* 2015; **43**(7): 1331–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
 135. Dai S, Wang C, Zhao X, et al.: **Cucurbitacin B: A review of its pharmacology, toxicity, and pharmacokinetics.** *Pharmacol Res.* 2023; **187**: 106587.
[PubMed Abstract](#) | [Publisher Full Text](#)
 136. Lin Y, Kotakeyama Y, Li J, et al.: **Cucurbitacin B Exerts Antiaging Effects in Yeast by Regulating Autophagy and Oxidative Stress.** *Oxid Med Cell Longev.* 2019; **2019**: 4517091. Epub 20190602. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 137. Botta G, Turn CS, Quintyne NJ, et al.: **Increased iron supplied through Fet3p results in replicative life span extension of Saccharomyces cerevisiae under conditions requiring respiratory metabolism.** *Exp Gerontol.* 2011 Oct; **46**(10): 827–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 138. Kirchman PA, Botta G: **Copper supplementation increases yeast life span under conditions requiring respiratory metabolism.** *Mech Ageing Dev.* 2007 Feb; **128**(2): 187–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 139. Jing JL, Ning TCY, Natali F, et al.: **Iron Supplementation Delays Aging and Extends Cellular Lifespan through Potentiation of Mitochondrial Function.** *Cells.* 2022 Mar 2; **11**(5). Epub 20220302. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 140. Johnson S, Imai SI: **NAD (+) biosynthesis, aging, and disease.** *F1000Res.* 2018; **7**: 132. Epub 20180201. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 141. Orlandi I, Alberghina L, Vai M: **Nicotinamide, Nicotinamide Riboside and Nicotinic Acid-Emerging Roles in Replicative and Chronological Aging in Yeast.** *Biomolecules.* 2020 Apr 15; **10**(4). Epub 20200415. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 142. Belenky P, Racette FG, Bogan KL, et al.: **Nicotinamide riboside promotes Sir2 silencing and extends lifespan via Nrk and Urh1/Pnp1/Meu1 pathways to NAD+.** *Cell.* 2007 May 4; **129**(3): 473–84.
[PubMed Abstract](#) | [Publisher Full Text](#)
 143. Dang W: **The controversial world of sirtuins.** *Drug Discov Today Technol.* 2014 06/01; **12**: e9–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 144. McClure JM, Wierman MB, Maqani N, et al.: **Isonicotinamide enhances Sir2 protein-mediated silencing and longevity in yeast by raising intracellular NAD+ concentration.** *J Biol Chem.* 2012 Jun 15; **287**(25): 20957–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 145. Kennedy BK, Austriaco NR Jr, Zhang J, et al.: **Mutation in the silencing gene S/R4 can delay aging in S. cerevisiae.** *Cell.* 1995; **80**(3): 485–96.
[PubMed Abstract](#) | [Publisher Full Text](#)
 146. Kennedy BK, Gotta M, Sinclair DA, et al.: **Redistribution of silencing proteins from telomeres to the nucleolus is associated with extension of life span in S. cerevisiae.** *Cell.* 1997; **89**(3): 381–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
 147. Sinclair DA, Guarente L: **Extrachromosomal rDNA circles—a cause of aging in yeast.** *Cell.* 1997 Dec 26; **91**(7): 1033–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
 148. Ha CW, Huh WK: **Rapamycin increases rDNA stability by enhancing association of Sir2 with rDNA in Saccharomyces cerevisiae.** *Nucleic Acids Res.* 2011 Mar; **39**(4): 1336–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 149. Flanagan PR, Liu NN, Fitzpatrick DJ, et al.: **The Candida albicans TOR-Activating GTPases Gtr1 and Rhb1 Coregulate Starvation Responses and Biofilm Formation.** *mSphere.* 2017 Nov-Dec; **2**(6). Epub 20171115. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 150. Stepień K, Wojdyla D, Nowak K, et al.: **Impact of curcumin on replicative and chronological aging in the Saccharomyces cerevisiae yeast.** *Biogerontology.* 2020 Feb; **21**(1): 109–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 151. Xiang L, Disasa D, Liu Y, et al.: **Gentirigioside B from Gentiana rigescens Franch Prolongs Yeast Lifespan via Inhibition of TORC1/Sch9/Rim15/Msn Signaling Pathway and Modification of Oxidative Stress and Autophagy.** *Antioxidants (Basel).* 2022 Nov 30; **11**(12). Epub 20221130. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 152. Liu Q, Cheng L, Matsuura A, et al.: **Gentiopicroside, a Secoiridoid Glycoside from Gentiana rigescens Franch, Extends the Lifespan of Yeast via Inducing Mitophagy and Antioxidative Stress.** *Oxid Med Cell Longev.* 2020; **2020**: 9125752. Epub 20200802. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 153. Liu Y, Liu Q, Chen D, et al.: **Inokosterone from Gentiana rigescens Franch Extends the Longevity of Yeast and Mammalian Cells via Antioxidative Stress and Mitophagy Induction.** *Antioxidants (Basel).* 2022 Jan 23; **11**(2). Epub 20220123. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 154. Sharma A, Kuhad A, Bhandari R: **Novel nanotechnological approaches for treatment of skin-aging.** *J Tissue Viability.* 2022; **31**(3): 374–86.
[PubMed Abstract](#) | [Publisher Full Text](#)
 155. Fonseca AP, Pizzol CD, Vanzo AC, et al.: **Antiaging effects of a skin care formulation containing nanoencapsulated antioxidants: A clinical, in vitro, and ex vivo study.** *J Cosmet Dermatol.* 2024; **23**(2): 510–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
 156. Rosen RS, Yarmush ML: **Current Trends in Anti-Aging Strategies.** *Annu Rev Biomed Eng.* 2023; **25**: 363–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
 157. Zhang Z, Yang R, Zi Z, et al.: **A new clinical age of aging research.** *Trends Endocrinol Metab.* 2024.
[Publisher Full Text](#)
 158. Benhamú B, Martín-Fontecha M, Vázquez-Villa H, et al.: **New Trends in Aging Drug Discovery.** *Biomedicines.* 2022 Aug 18; **10**(8). Epub 20220818. eng.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 159. Huang A, Huo Y, Zhong Y, et al., editors.: **AI Technology for Anti-Aging: an Overview.** 2023 *International Conference on Intelligent Supercomputing and BioPharma (ISBP)*; 2023 6–8 Jan. 2023.
 160. Lam YT, Stocker R, Dawes IW: **The lipophilic antioxidants alpha-tocopherol and coenzyme Q10 reduce the replicative lifespan of Saccharomyces cerevisiae.** *Free Radic Biol Med.* 2010 Jul 15; **49**(2): 237–44.
[PubMed Abstract](#) | [Publisher Full Text](#)

161. Jung PP, Zhang Z, Paczia N, *et al.*: **Natural variation of chronological aging in the *Saccharomyces cerevisiae* species reveals diet-dependent mechanisms of life span control.** *NPJ Aging Mech Dis.* 2018; **4**(1): 3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
162. Teng X, Dayhoff-Brannigan M, Cheng WC, *et al.*: **Genome-wide consequences of deleting any single gene.** *Mol Cell.* 2013 Nov 21; **52**(4): 485–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
163. Warringer J, Zörgö E, Cubillos FA, *et al.*: **Trait variation in yeast is defined by population history.** *PLoS Genet.* 2011 Jun; **7**(6): e1002111.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:     

Version 2

Reviewer Report 24 January 2025

<https://doi.org/10.5256/f1000research.175742.r350456>

© 2025 Dang W. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Weiwei Dang 

Huffington Center On Aging and Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

The manuscript titled "**Exploring the Anti-Aging Potential of Natural Products and Plant Extracts in Budding Yeast**" provides an in-depth review of the role of *Saccharomyces cerevisiae* as a model organism in aging research. The key focus areas include:

- **Natural Products and Their Mechanisms:** The review discusses several natural compounds and plant extracts that influence aging pathways in yeast, organized according to their impact on chronological lifespan (CLS) and replicative lifespan (RLS).
- **Molecular Pathways:** Key pathways involved in yeast aging, such as the TOR/Sch9 and RAS/AC/PKA pathways, are extensively reviewed in relation to their conserved roles in both yeast and human aging processes.
- **Experimental Considerations:** The manuscript highlights the strengths and limitations of using yeast as a model, such as its genetic tractability versus its limitations in modeling complex multicellular aging processes.
- **Emerging Trends:** A new section in the revised manuscript explores novel approaches in anti-aging research, including nanotechnology, artificial intelligence, and nutrigenomics.
- **Future Directions:** It identifies areas needing further exploration, such as understanding the genetic interactions with natural products and optimizing experimental conditions for better translational outcomes.

Strengths of the Manuscript

1. **Comprehensive Literature Review:** The manuscript effectively compiles and organizes a wide range of studies related to natural products' effects on yeast aging.
2. **Revised Structural Organization:** Following peer reviews, the manuscript now presents data in a more logical flow by categorizing compounds under CLS, RLS, or both.
3. **Enhanced Figures and Tables:** The revised version includes expanded tables summarizing natural product actions, their sources, dosages, and effects, making the content more accessible.
4. **Addressing Reviewer Comments:** The authors have been responsive to reviewer feedback, incorporating their suggestions to improve readability and focus.

Weaknesses of the Manuscript

1. **Terminology Issue:** The manuscript refers to CLS and RLS as "patterns" of aging; however, it would be more accurate to refer to them as distinct **models** of yeast aging, reflecting their independent mechanistic underpinnings.
2. **Overlapping Concepts:** While the authors have reorganized content, there are still sections where CLS and RLS mechanisms are described with some redundancy, which could be streamlined further.
3. **Lack of Human Translational Insights:** Although yeast is an excellent model, further discussion on how the findings translate to human aging interventions would improve the manuscript's impact.
4. **Experimental Variability:** The manuscript should emphasize more on the influence of yeast strain background, auxotrophic mutations, and media composition on the reproducibility of findings.

I hope that the authors can address these remaining weaknesses in a minor revision.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Yeast aging, epigenetics, chromatin, stem cell aging, senescence, sirtuins

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 16 January 2025

<https://doi.org/10.5256/f1000research.175742.r352761>

© 2025 Manisekaran H. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Hemagirri Manisekaran 

Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia, Pulau Pinang,

Malaysia

Summary of the Article

The paper titled "Exploring the anti-aging potential of natural products and plant extracts in budding yeast *Saccharomyces cerevisiae*: A review" discusses the role of natural products, particularly plant extracts, in combating aging, using the model organism *Saccharomyces cerevisiae*. The authors explore various biochemical pathways related to aging, such as the target of rapamycin (TOR) and protein kinase A (PKA) signaling pathways. The review highlights historical uses of plant-derived substances for medicinal purposes and emphasizes the need for further research into natural products as potential anti-aging therapies.

Overall Assessment: Yes, the paper is well-structured and presents a comprehensive review of the anti-aging potential of natural products and plant extracts in *Saccharomyces cerevisiae*.

Comprehensiveness of the Topic: Yes

The review discusses the topic comprehensively within the context of current literature. It effectively covers various aspects of aging and natural products.

Factual Statements and Citations: Yes

All factual statements are correct and adequately supported by citations from relevant literature. The authors have done a commendable job in referencing key studies.

Accessibility of Language: Yes

The review is written in accessible language, making it understandable for a wide audience, including those who may not be specialists in the field.

Appropriateness of Conclusions: Partly

The conclusions drawn about the potential of natural products as anti-aging therapies are valid but could be more comprehensive. The authors should discuss limitations in current research and propose specific future research directions to enhance their conclusions.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Aging

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 15 January 2025

<https://doi.org/10.5256/f1000research.175742.r357244>

© 2025 Eigenfeld M. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Marco Eigenfeld 

Medical University Graz, Graz, Australia

Abstract

The sentence, "The budding yeast *Saccharomyces cerevisiae* has been, and continues to be, an indispensable model organism in the field of biomedical research for discovering the molecular basis of aging *S. cerevisiae* has preserved nutritional signaling pathways (such as the target of rapamycin (TOR)-Sch9 and the Ras-AC-PKA (cAMP-dependent protein kinase) pathways, and shows two distinct aging paradigms chronological life span (CLS) and replicative life span (RLS)", is overly long, grammatically incorrect, and contains repetitive wording such as "pathways." Breaking this sentence into shorter, more focused sentences would improve readability. For instance, you could restructure it as follows: "The budding yeast *Saccharomyces cerevisiae* has long been an indispensable model organism for studying the molecular basis of aging in biomedical research. It has preserved nutritional signaling pathways, such as the target of rapamycin (TOR)-Sch9 and the Ras-AC-PKA (cAMP-dependent protein kinase) pathways. *S. cerevisiae* also demonstrates two distinct aging paradigms: chronological life span (CLS) and replicative life span (RLS)." Additionally, the abstract would benefit from including specific examples of natural compounds rather than relying on the general term "natural compounds." Incorporating examples like resveratrol, quercetin, or berberine (if relevant) would make the abstract more engaging and provide readers with a clearer understanding of the focus of the study.

Introduction

Rather than simply stating that aging is a major risk factor, I recommend emphasizing the bidirectional relationship: aging promotes diseases, and diseases, in turn, can exacerbate aging. This perspective would provide a more comprehensive understanding of the interplay between aging and disease.

The sentence starting with "However, life style associated anti-aging ..." would benefit from being simplified by dividing it into two sentences. This would enhance readability and make the point more accessible to readers.

For the statement, "Historically, medicinal plants have been used ...", and the one referencing "The oldest records dating back to around 2600 BCE, ...", please include at least one supporting reference to strengthen the claims and provide credibility to these historical assertions.

In my opinion, the section beginning with "It is no surprise that traditional ..." should be shortened. As it stands, this part is very broad, covering historical, pharmacological, and regulatory topics without a clear narrative structure. Since this section is in the introduction, it should aim to guide the reader toward the paper's central topic. Currently, it lacks a clear

connection to anti-aging research, which is the main focus of the paper. Condensing this section and tying it more directly to the context of anti-aging potential in natural products and plant extracts would improve its relevance.

On the other hand, the final section of the introduction fits perfectly within the context and scope of the paper and provides a clear lead-in to the study. Emphasizing this alignment throughout the introduction would enhance the overall cohesion of the manuscript.

The budding yeast *Saccharomyces cerevisiae*– A simple eukaryotic model to study aging

I would recommend using the term “membrane-enclosed” rather than “membrane-bound” when describing organelles. The term “membrane-bound” could imply that the organelles are physically anchored or fixed in place, which may lead to misinterpretation. “Membrane-enclosed” more accurately conveys that these organelles are surrounded by a membrane without suggesting spatial restriction.

The size of yeast needs to be more precise. For ovoid cells, it would be important to provide both diameters (length and width) to ensure clarity and scientific accuracy.

Additionally, the statement “The budding yeast was the first eukaryotic ...” and “Most interestingly, yeast share several homologous” requires a proper reference to support this claim. Furthermore “The budding yeast has long been used as a ...” as well as in multiple other passages, the authors make claims and refer to other general statements without supporting references. Please revise accordingly.

To improve readability and avoid redundancy, I suggest varying the starting words in the yeast paragraph. Currently, the repeated use of “The” and “Yeast” at the beginning of multiple sentences makes the section feel monotonous. In the first paragraph: The ... Yeast ... Yeast ... The ... The ... The ... The ... The ... Interestingly ... The; Consider using alternative phrasing or reworking sentence structures to create a more engaging flow.

The section starting with “These features make yeast an ideal model organism ...” and the subsequent discussion of its limitations needs to be restructured. As it currently stands, the focus shifts heavily toward the limitations, leaving a somewhat negative impression about the use of yeast as a model organism. I recommend balancing the argument by first emphasizing the unique advantages of yeast and then framing the limitations more constructively, such as highlighting areas where complementary models or additional approaches may be necessary, or why yeast is ideal for anti-aging substance tests. This would ensure the argument remains balanced and aligns with the overall positive perspective on yeast as a valuable tool in aging research.

Replicative lifespan (RLS) and chronological lifespan (CLS)

The section discussing replicative lifespan (RLS) and chronological lifespan (CLS) could benefit from some adjustments to improve clarity and relevance. In the second line, the authors mention the number of bud scars without explaining that the bud scar remains after cytokinesis. Including this detail would help readers who might not already be familiar with this concept.

In the sentence beginning “In old mother cells, the actin cytoskeleton...,” it would be helpful to include a reference for this statement, as well as for the subsequent sentence. These references are particularly important because they provide context for understanding the limited RLS of yeast, which is otherwise considered theoretically immortal.

The following two paragraphs delve deeply into extrachromosomal rDNA circles (ERCs). It's worth considering whether this level of detail is necessary. How do these paragraphs connect to the paper's main topic and title? If ERCs are relevant to the anti-aging potential of the extracts discussed later, this connection should be made explicit. Otherwise, these paragraphs might be overly detailed and disrupt the flow of the paper. If they are not crucial, I would suggest removing them to streamline the narrative.

The sentence "In worms, flies, and mice, the key..." and similar statements, such as "In addition, stationary phase cells show..." lack references. Since this is a review article, it's essential to provide references for such claims. While this issue recurs throughout the text, I won't list every instance here. I strongly encourage the authors to carefully review the entire manuscript and ensure all statements are properly supported by references. This is especially important in a review, where all information should be accurately cited rather than assumed to be common knowledge. The details on diauxic effects and growth curves may not be essential for explaining CLS. Overall, the CLS section, like the RLS section, feels quite long and lacks a clear connection to the review's main topic. I recommend condensing these sections and focusing more on how they relate to the central theme. There are already numerous review papers on yeast lifespan that could be referenced instead of including extensive background information here. This would help maintain a logical flow and keep the focus on the specific objectives of the paper.

Conserved nutrient sensing aging regulatory pathways in budding yeast

This section is well-written and provides a concise summary of key knowledge that is essential for understanding the mechanisms discussed later in the manuscript.

Anti-aging studies of natural products and plant extracts in the budding yeast *S. cerevisiae* as a model

On page 10 of the review, the main topic is finally introduced, addressing a fascinating and novel area of knowledge. However, there are some aspects that could benefit from improved clarity and scientific rigor. For instance, the opening sentence refers to "several," but no examples or references are provided. To ensure scientific accuracy and strengthen the credibility of the text, including specific examples or citations would be helpful.

Similarly, the sentence beginning with "Natural compounds, which..." would benefit from the inclusion of examples, as it feels incomplete. In the subsequent sentence, the discussion becomes more specific by focusing on plant-isolated compounds, which creates some inconsistency. If the terms "natural compounds" and "plant-isolated compounds" are intended to be synonymous, it would be better to use just one term consistently throughout this section to avoid confusion. Later, the word "various" is used, which lacks precision. Since eight mechanisms are mentioned, it would be clearer to state "eight mechanisms" explicitly. Such specificity would enhance the scientific rigor of the text and make it easier for readers to follow.

Natural products/plant extracts vs. CLS

The authors begin again with the term "several studies" but fail to reference specific studies to support the statement that these studies explored the mentioned topic. Providing appropriate citations would greatly strengthen the credibility and scientific rigor of the manuscript. Furthermore, in Table 1, the authors appear to assume that all yeasts are *Saccharomyces* yeasts, which is not accurate. It would be important to specify that the yeasts in question are *Saccharomyces* strains or provide more precise terminology to avoid potential misunderstandings. Additionally, throughout the manuscript, there is a lack of clarity when referring to yeast. The authors are encouraged to use more specific terminology, such as *Saccharomyces cerevisiae*,

whenever applicable. This will not only improve precision but also help readers better understand the scope and focus of the discussion.

In following I will not include all subsection names:

In the section on "Acetyl L-carnitine," the authors refer to "Researchers have shown..." without citing specific studies or providing detailed evidence. Including references to support this statement would add credibility and depth to the discussion. Additionally, there is a typographical error in this section where "Ca²⁺" is written without the superscript. Correcting this will improve the professionalism and accuracy of the presentation.

In the astaxanthin section, the authors refer to a study by Sudarshan et al., but the reference number is missing at the end of the sentence. Including the reference number is important for accessibility, as it makes it easier for readers to locate the source without having to cross-reference the name with the reference list. The same issue arises at the end of the section, where a reference number should also be included.

Regarding the compound artesunate, its inclusion raises an important question: if the compound is semi-synthetic, why is it included in a paper focusing on compounds extracted from natural sources? This point needs clarification to align the discussion with the scope of the paper. Additionally, this section suffers from a lack of references. While the text mentions "Previous studies have shown" in the plural form, only one reference is provided at the end. To maintain scientific rigor, it is necessary to either cite multiple studies or adjust the wording to reflect the actual number of cited works.

In the section discussing Betulinic acid, the authors state that it is present in some plant species but do not provide examples. Naming specific plant species where Betulinic acid is found would add valuable detail and context for the readers, enhancing the depth of the discussion.

In the section focusing on citrus, the issue of plural wording remains unresolved. If writing in plural, more than one reference must be provided to substantiate the claim. Additionally, it would be helpful to explain why ROS accumulation is prevented, as this adds clarity and context to the discussion.

In the section on "4-N-furfurylcytosine," the authors should clarify why viability is increased and why mitochondrial activity is boosted. These are important mechanistic details that should not be omitted. Furthermore, the source of isolation for this compound is not mentioned, which detracts from the manuscript's alignment with the scope of natural products.

The section on "Galactan exopolysaccharide" refers to a study without citing it. Proper citation is necessary here, and the mechanism of action for this compound should also be explained to provide a deeper understanding of its effects.

In the discussion of Ginsenoside, the authors use the plural form to refer to studies but cite only a single reference. This inconsistency should be corrected either by providing additional references or by adjusting the language to the singular form.

The section on "Lithocholic acid" has a similar reference issue, as the authors fail to include the reference number for the study by Beach et al.

In the section on Magnolol, it is unclear whether the reference cited is the only available one. Including a second reference, if available, would enhance the accuracy and credibility of this section. More broadly, sections that rely on a single reference would benefit from being expanded with additional supporting studies.

For the sections on Myricetin and Spermidine, the citation issue persists as above, with references not being properly cited. The same applies to Quercetin, and additionally, the discussion on why ROS levels are reduced is missing and should be included to strengthen the argument.

The section on Almond extract also has issues with plural language and missing references. Moreover, it is unclear why the alphabetical order begins again in this section, which disrupts the structure and flow of the manuscript.

The inclusion of a section titled "Natural products/plant extracts vs. RLS" in the list is confusing and seems out of place. Is maybe this a new header? Then please increase text size. The same with RLS&CLS.

The alphabetical order restarts here without explanation, creating the impression of rushed revisions. The manuscript would benefit from a thorough restructuring to ensure consistent organization. The authors should revise the manuscript as a whole to address these recurring issues with references, singular/plural discrepancies, and the alphabetical ordering of sections.

Overall comments

To improve the clarity and coherence of the manuscript, I recommend restructuring the listing of compounds in a systematic and consistent way. Each compound should be presented with the following elements:

1. **Source:** Clearly state from which natural source the compound is isolated. This ensures alignment with the scope of the manuscript and provides essential context for each compound.
2. **Effect:** Describe the specific biological or physiological effect of the compound.
3. **Mechanism:** Provide an explanation of how the observed effect is achieved, ideally supported by evidence from studies.

Currently, many compounds are missing one or more of these critical aspects, which makes the listing incomplete and inconsistent. Ensuring all three elements are addressed for each compound will significantly enhance the comparability and scientific rigor of the discussion.

Moreover, some compounds have been discussed in the context of key pathways such as TORC1/Sch9/Rim15/Msn signaling, RAS-AC-PKA pathway, Sir2-dependent pathway, NAD⁺-salvage pathway, and Uth1/TOR signaling. For example Acetyl-L-carnitine, astaxanthin, betulinic acid, galactan exopolysaccharide, magnolol, myricetine. These pathways appear central to the manuscript's main point, yet their discussion is sparse and insufficiently integrated. To better support the main argument, each compound should be explicitly linked to one or more of these pathways whenever applicable. This will tie the individual sections together and link to the introduction of the pathways.

After reviewing the manuscript again, the section on ERCs is unclear, as it is never referenced in the later context. Additionally, RLS and CLS are described in excessive detail, which seems unnecessary for the later sections. I would like to see more focus on how the compounds impact

RLS and CLS. These details, which would provide valuable new insights for a review, are missing from the compound descriptions. Specifically, quantitative data such as how many additional buddings are possible due to the compounds or how many hours the CLS is extended by their antioxidative effects would greatly enhance the manuscript.

Is the topic of the review discussed comprehensively in the context of the current literature?

Partly

Are all factual statements correct and adequately supported by citations?

Partly

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Investigating the mechanisms of yeast aging and yeast physiology, with a focus on the interplay between aging and protein synthesis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Reviewer Report 26 March 2024

<https://doi.org/10.5256/f1000research.155136.r253397>

© 2024 Hartman J. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



John Hartman

Genetics, University of Alabama-Birmingham, Birmingham, AL, 35294-0024, USA

The authors may want to consider more precise and directional adjectives, such as enhance, suppress, augment, alleviate, etc. Use of the word 'ameliorate' to qualify various biological effects, seemed vague, inconsistent, and sometimes incorrect. My suggestion would be to carefully proof-read again for grammar in places but also for biological clarity, for example, about relationships between TOR signaling and respiration.

Overall, I thought the review topic was very interesting - the authors have assembled a collection of papers about natural products (NPs) where biological activities have been studied using paradigms (RLS and CLS) of yeast aging.

The abstract and introduction could be greatly enhanced by removing much of the philosophical and physiological descriptions of aging, how it's fundamental to several diseases, and the utility and experimental benefits of model organisms, all of which have been made many times and are thus an unnecessary distraction. If condensed to a couple sentences and citations there would be much space cleared to focus more on the topic at hand which is already very rich and extensive and could stand to be expanded upon and further detailed.

Fig. 1 is awkward IMO (in a BioRender sort of way) and it's not really needed. To regain that space and maintain reader attention, a simple brief description of RLS and CLS would do (with just a few of many possible citations that could support the rare reader who may not be already familiar).

It would be helpful to organize the paper according to which NPs were studied in the context of RLS, CLS, or both. The models are quite different, though they involve related mechanisms as the authors point out. Clarifying and distinguishing (or unifying) between the RLS/CLS models over the course of the MS would be of interest (more to come on this and other factors that could be better organized in order to increase the impact of the work).

Fig. 2 is helpful, but should be expanded with regard to the genes and pathways (and the page space) and doesn't need to be rendered as an actual cell if removing the picturesque constraints of the cell and organelles would provide more flexibility to communicate important information about the literature.

The "conserved nutrient sensing aging regulatory pathways" section is critical and could be expanded substantially. "Conserved" presumably means "between" yeast and humans? This section seems woefully under-cited. If possible, all of the genes mentioned in the NP papers should be incorporated into this section and Fig. 2 and related to one another, which would ultimately help to relate the NPs to each other regarding their influences on cellular aging. There is an opportunity here to relate the yeast pathways to the human pathways (i.e. to relate the conserved pathways), and ultimately to suggest how some of the NPs, which influence yeast aging, could be related to benefits they are thought to putatively have in humans. I think that opportunity wasn't really capitalized on but would be great if the authors could. This would provide demonstrations for the significance of the topic and the importance of the review as a starting point to increase knowledge about relationships between NPs, yeast aging models, and human age-related disease.

The "Anti-Aging studies "of NPs" in *S. cerevisiae*" section should mention NPs in the section subtitle (just for clarity).

Rather than just a list of NPs - this section would be much more useful if organized by important factors. I'm not sure exactly how to do it, but a table would very helpful for handling this aspect. Strategies that could be used to organize this section include alphabetical order, whether influences are on CLS, RLS, or both; class of compounds; relevant sources of the compounds (foods, alternative medicines, natural metabolism, microbiome, etc); whether they have known or

suspected effects on human health; MOA or genes and pathways they are thought to act or interact with; whether the NPs are easily obtained for research purposes (i.e. where to buy them); other factors that the authors may be aware of.

A table that synthesizes and distills the important factors relevant to each NP should be created (as also suggested by Reviewer 1). The table should have a field dedicated to each factor (see a few suggestions in paragraph above) and have concise record entries for each NP - one of the fields should be for the references for convenient lookup of information in the table context. If provided as a spreadsheet, it would be particularly useful.

Just my personal opinion, but I didn't see how descriptions of the advantages of yeast, emerging trends, cutting edge techniques, or future directions would be as helpful as more detail and better organization about the NPs, in-depth summary about the literature where yeast have been used to study them, and if possible where they are are also relevant to human and/or specific age-related diseases.

About "conclusions drawn being 'partly' supported" there can be large effects on CLS deriving from differing auxotrophic background of yeasts strain and media recipes. Things like glucose concentration, whether the media is buffered, amino acid compositions, the presence of ammonium sulfate, rich vs. synthetic/defined media, the list goes on. The interactions between the NPs and genetic background was discussed in the review, but these same types of interactions exist with auxotrophic mutations and media composition (which can vary dramatically between studies). This fact should be briefly mentioned in the manuscript and ideally accounted for in the proposed table by indicating the strain, auxotrophic background and media used in the studies employing particular NPs. Additives like H₂O₂ that are used to enhance characterization are mentioned in places and could also be accounted for in the table.

I appreciate the authors' efforts and insights hope they find this feedback useful.

References

1. Santos SM, Laflin S, Broadway A, Burnet C, et al.: High-resolution yeast quiescence profiling in human-like media reveals complex influences of auxotrophy and nutrient availability. *Geroscience*. 2021; **43** (2): 941-964 [PubMed Abstract](#) | [Publisher Full Text](#)
2. Smith DL, Maharrey CH, Carey CR, White RA, et al.: Gene-nutrient interaction markedly influences yeast chronological lifespan. *Exp Gerontol*. 2016; **86**: 113-123 [PubMed Abstract](#) | [Publisher Full Text](#)
3. Sun S, Baryshnikova A, Brandt N, Gresham D: Genetic interaction profiles of regulatory kinases differ between environmental conditions and cellular states. *Mol Syst Biol*. 2020; **16** (5): e9167 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the topic of the review discussed comprehensively in the context of the current literature?

Partly

Are all factual statements correct and adequately supported by citations?

Partly

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: yeast genetics, human disease models, CLS

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 08 Dec 2024

Tewin Tencomnao

The authors may want to consider more precise and directional adjectives, such as enhance, suppress, augment, alleviate, etc. Use of the word 'ameliorate' to qualify various biological effects, seemed vague, inconsistent, and sometimes incorrect. My suggestion would be to carefully proof-read again for grammar in places but also for biological clarity, for example, about relationships between TOR signaling and respiration.

Response: We thank you for your suggestions on the precise usage of adjectives and grammar in this manuscript. As suggested, we have carefully proofread the document and considered the usage of more precise and directional adjectives throughout the revised manuscript.

Overall, I thought the review topic was very interesting - the authors have assembled a collection of papers about natural products (NPs) where biological activities have been studied using paradigms (RLS and CLS) of yeast aging.

The abstract and introduction could be greatly enhanced by removing much of the philosophical and physiological descriptions of aging, how it's fundamental to several diseases, and the utility and experimental benefits of model organisms, all of which have been made many times and are thus an unnecessary distraction. If condensed to a couple sentences and citations there would be much space cleared to focus more on the topic at hand which is already very rich and extensive and could stand to be expanded upon and further detailed.

Response: As suggested by the reviewer, the philosophical and physiological descriptions of aging are removed from the abstract and introduction of the revised manuscript. Additionally, the review has been focused on the natural products (please see Introduction).

Fig. 1 is awkward IMO (in a BioRender sort of way) and it's not really needed. To regain that space and maintain reader attention, a simple brief description of RLS and CLS would do (with just a few of many possible citations that could support the rare reader who may not be already familiar).

Response: As suggested by the reviewer, we have included additional information on CLS and RLS along with their respective citations. However, we believe that inclusion of Figure 1 may help readers, particularly budding yeast researchers working on anti-aging research,

and facilitate an easier understating of the concepts of CLS and RLS.

It would be helpful to organize the paper according to which NPs were studied in the context of RLS, CLS, or both. The models are quite different, though they involve related mechanisms as the authors point out. Clarifying and distinguishing (or unifying) between the RLS/CLS models over the course of the MS would be of interest (more to come on this and other factors that could be better organized in order to increase the impact of the work).

Response: We appreciate your insightful suggestion and we have reorganized the anti-aging effects of natural products according to the relevance of CLS or RLS or both. We do believe that this reorganization further enhances the impact of work.

Fig. 2 is helpful, but should be expanded with regard to the genes and pathways (and the page space) and doesn't need to be rendered as an actual cell if removing the picturesque constraints of the cell and organelles would provide more flexibility to communicate important information about the literature.

Response: As suggested by the reviewer, Figure 2 is improved in the revised manuscript.

The "conserved nutrient sensing aging regulatory pathways" section is critical and could be expanded substantially. "Conserved" presumably means "between" yeast and humans? This section seems woefully under-cited. If possible, all of the genes mentioned in the NP papers should be incorporated into this section and Fig. 2 and related to one another, which would ultimately help to relate the NPs to each other regarding their influences on cellular aging. There is an opportunity here to relate the yeast pathways to the human pathways (i.e. to relate the conserved pathways), and ultimately to suggest how some of the NPs, which influence yeast aging, could be related to benefits they are thought to putatively have in humans. I think that opportunity wasn't really capitalized on but would be great if the authors could. This would provide demonstrations for the significance of the topic and the importance of the review as a starting point to increase knowledge about relationships between NPs, yeast aging models, and human age-related disease.

Response: Thank you for your insightful suggestion. The section entitled "conserved nutrient-sensing aging regulatory pathways" has been revised with sufficient citations for each of the singling pathways discussed in the review.

The "Anti-Aging studies "of NPs" in *S. cerevisiae*" section should mention NPs in the section subtitle (just for clarity).

Response: As suggested, the tile of the section has been changed to "Anti-aging studies of natural products and plant extracts in the budding yeast *S. cerevisiae* as a model."

Rather than just a list of NPs - this section would be much more useful if organized by important factors. I'm not sure exactly how to do it, but a table would very helpful for handling this aspect. Strategies that could be used to organize this section include alphabetical order, whether influences are on CLS, RLS, or both; class of compounds; relevant sources of the compounds (foods, alternative medicines, natural metabolism, microbiome, etc); whether they have known or suspected effects on human health; MOA or genes and pathways they are thought to act or interact with; whether the NPs are easily obtained for research purposes (i.e. where to buy them); other factors that the authors may

be aware of.

Response: We thank you for your valuable suggestions on the organization of natural products. As suggested, the section on the natural products and plant extracts has been reorganized, with the anti-aging studies now arranged alphabetically in the revised version of the manuscript.

A table that synthesizes and distills the important factors relevant to each NP should be created (as also suggested by Reviewer 1). The table should have a field dedicated to each factor (see a few suggestions in paragraph above) and have concise record entries for each NP - one of the fields should be for the references for convenient lookup of information in the table context. If provided as a spreadsheet, it would be particularly useful.

Response: Thank you for your suggestion. A table summarizing the natural products and plant extracts including their source, chemical class, dosage used, growth medium used for aging studies, yeast strain used, and their anti-aging mechanisms, has been included in the revised manuscript. Please refer to table 1, 2, and 3

Just my personal opinion, but I didn't see how descriptions of the advantages of yeast, emerging trends, cutting edge techniques, or future directions would be as helpful as more detail and better organization about the NPs, in-depth summary about the literature where yeast have been used to study them, and if possible where they are also relevant to human and/or specific age-related diseases.

Response: We thank you for your insightful suggestions on the importance of adding in depth literature on the natural products and the reorganization of the natural products section. We have reorganized the revised manuscript and included an in-depth summary of natural products.

About "conclusions drawn being 'partly' supported" there can be large effects on CLS deriving from differing auxotrophic background of yeasts strain and media recipes. Things like glucose concentration, whether the media is buffered, amino acid compositions, the presence of ammonium sulfate, rich vs. synthetic/defined media, the list goes on. The interactions between the NPs and genetic background was discussed in the review, but these same types of interactions exist with auxotrophic mutations and media composition (which can vary dramatically between studies). This fact should be briefly mentioned in the manuscript and ideally accounted for in the proposed table by indicating the strain, auxotrophic background and media used in the studies employing particular NPs. Additives like H₂O₂ that are used to enhance characterization are mentioned in places and could also be accounted for in the table.

Response: We briefly mentioned in the manuscript how different factors such as carbon sources, amino acid composition, pH of the growth medium affects the CLS. Additionally, we have included a table that accounts for the strain background, media used in anti-aging studies of natural products/plant extract.

Competing Interests: No competing interests were disclosed.

<https://doi.org/10.5256/f1000research.155136.r212350>

© 2023 Sirasanagandla S. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Srinivasa Rao Sirasanagandla 

Department of Human & Clinical Anatomy, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman

The current review presents a summary of aging and the use of *Saccharomyces cerevisiae* as a model organism for anti-aging research. It's informative and well-structured, making it suitable for readers interested in the topic. Here are a few suggestions for elevating the quality of this review.

- In the abstract, authors should provide a clear overview of the research focus, its significance, and what readers can expect from the review. Begin with a clear statement of the objective or focus of the research. For example, "This review aims to explore the anti-aging properties of several natural products and phytoextracts using the budding yeast *Saccharomyces cerevisiae* as a model organism." Explain the significance of studying aging and anti-aging research. Highlight the Contribution. Include a statement about what readers can expect from the review.
- In the introduction sections, please cite the figures 1 and 2.
- It would be more informative if authors had provided a table summarizing the action of natural products and/or plant extracts.
- The authors should also highlight the advantages and disadvantages of using yeast as a model for anti-aging research.
- The authors should include a section on emerging trends that focuses on identifying emerging trends and cutting-edge techniques in the study of anti-aging compounds.
- A distinct section focusing on future directions that need further exploration in the field should also be added.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Natural compounds against the environmental pollutant induced toxicity, radiological anatomy, morphological variations

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 08 Dec 2024

Tewin Tencomnao

- In the abstract, authors should provide a clear overview of the research focus, its significance, and what readers can expect from the review. Begin with a clear statement of the objective or focus of the research. For example, "This review aims to explore the anti-aging properties of several natural products and phytoextracts using the budding yeast *Saccharomyces cerevisiae* as a model organism." Explain the significance of studying aging and anti-aging research. Highlight the Contribution. Include a statement about what readers can expect from the review.

Response: We thank reviewer for the insightful comment on the abstract. We have revised the abstract by incorporating a clear overview of the research focus and the significance of the aging and anti-aging research.

- In the introduction sections, please cite the figures 1 and 2.

Response: We apologies for overlook in not citing the figures. We have cited Figures 1 and 2 at appropriate sections of the revised manuscript.

- It would be more informative if authors had provided a table summarizing the action of natural products and/or plant extracts.

Response: As suggested by the reviewer, we have summarized the anti-aging molecular mechanisms of actions of natural products and plant extracts in Tables 1, 2, and 3.

- The authors should also highlight the advantages and disadvantages of using yeast as a model for anti-aging research.

Response: "The main advantages of using the yeast *Saccharomyces cerevisiae* in aging research are that it is a unicellular eukaryote that exhibits characteristic features such as rapid growth, inexpensive, and ease of genetic manipulation, allowing to conduct experiments quickly and study the effects of specific genes on aging. Several of the cellular processes and metabolic pathways, including aging, are conserved between *S. cerevisiae* and humans. These features make yeast an ideal model organism for the high-throughput screening of identifying genes and chemical compounds associated with aging. However, the use of yeast has some limitations. For example, its unicellular nature limits its ability to model complex multicellular organisms and tissue-specific aging processes in humans. Additionally, some post-translational modifications that occur in humans do not occur in yeast, and yeast metabolism significantly differs from humans, which may limit applicability

if certain findings to human aging research.” This information has been included in the section titled “The budding yeast *Saccharomyces cerevisiae* – A simple eukaryotic model to study aging” in the revised version of the manuscript.

- The authors should include a section on emerging trends that focuses on identifying emerging trends and cutting-edge techniques in the study of anti-aging compounds.

Response: We thank reviewers for their valuable suggestion on the necessity of adding a section on the emerging trends in the study of anti-aging compounds. As suggested, a separate section is included in the revised manuscript.

- A distinct section focusing on future directions that need further exploration in the field should also be added.

Response: A separate section compiling both emerging trends and future developments in the anti-aging research are included in the revised manuscript.

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research