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Research Article

# Rapamycin as Anti-Aging Treatment: A Literature Review

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## Abstract

Several biological theories of aging are the FOXO3/Sirtuin pathway which may be responsive to caloric restriction, the growth hormone/IGF-1-like pathway and the electron transport chain in mitochondria and in chloroplasts. One variant of FOXO3 has been demonstrated to be related to life span in people. This variant is found in many centenarians from various ethnic groups worldwide. It is being regulated by mTORC1 and mTORC2 and assumes a significant role in controlling cell growth. mTOR is a protein found in humans that is an appealing target for aging studies. It can possibly influence processes that could primarily affect the body and it also hastens aging in various life forms such as worms and mammals. mTORC2 might be repressed by long-term rapamycin treatment. This study aims to review current evidence on the anti-aging properties of rapamycin. Rapamycin demonstrates significant promise in animal models as a drug for the treatment of age-related diseases. However, the significant reactions limit its long-term use in people. Further research will be required to know if rapamycin will be helpful to human lifespan and protect against age-related diseases.

**Keywords:** Rapamycin; Anti-Aging; Pathway

## Introduction

Aging is one of the major risk factors for the majority of human diseases. The exact causes of aging are unknown, yet current hypotheses are focused on the damage concept. Externally-induced damage like DNA mutations may cause the failure of several biological processes in the body. Internal processes in the body such as the shortening of DNA telomeres may lead to aging [1].

Several biological theories of aging are the FOXO3/Sirtuin pathway which may be responsive to caloric restriction, the growth hormone/IGF-1-like pathway and the electron transport chain in mitochondria and in chloroplasts.2 FOXO3 is Forkhead box O3, otherwise called FOXO3 or FOXO3a. It is a human protein that is encoded by the FOXO3 gene. One variant of FOXO3 has been demonstrated to be related to life span in people. This variant is found in many centenarians from various ethnic groups worldwide. It is being regulated by mTORC1 and mTORC2 and assumes a significant role in controlling cell growth [2]. mTOR is otherwise known as the mechanistic target of rapamycin (mTOR) or the mammalian target of rapamycin, though it may also be known as FK506-binding protein 12-rapamycin-associated protein 1 (FRAP1) [3]. It is a protein found in humans that is encoded by the MTOR gene. It is a serine/threonine-protein kinase that controls cell growth and proliferation, cell movement, cell survival, protein synthesis, autophagy and transcription [4]. It is considered as a member of the phosphatidylinositol 3-kinase-related protein family [5].

mTOR is a kinase that is a member of the phosphatidylinositol-3 kinase-related kinases (PIKKs) family, a group of serine/threonine protein kinases, with a structure that is similar to the group of lipid kinases, PI3Ks. These kinases have diverse functions, yet are proteins with a common domain structure. PIKKs have four domains at the protein level, which has set them apart from the other protein kinases. mTOR is an appealing target for aging studies. It can possibly influence processes that could primarily affect the body and it also hastens aging in various life forms such as worms and mammals. It was discovered in 1994 as a protein that is bound by rapamycin. It was soon found out to be the serine/threonine kinase that regulates the reaction of eukaryote cells to growth factors, nutrients, and cellular energy [5].

**Figure 1:** The four domains of mTOR at the protein level. Lybbar12 [CC BY-SA 3.0 (https://creativecommons.org/licenses/by-sa/3.0)]

mTOR controls cell metabolism, growth, and processes. It is affected by hormonal secretion, cytokines and growth factors. It is associated with age-related diseases such as metabolic syndrome, heart disease, dementia, osteoporosis, and atherosclerosis. Its inhibition suppresses the conversion of cells into senescence [6]. mTOR creates two major complexes: mTORC1 and mTORC2. It is a 289-kDa kinase that is 40% similar to the TOR proteins of Saccharomyces cerevisiae and is highly conserved among eukaryotes [7]. mTORC1 can be inhibited by rapamycin through specific binding to fkbp12, prompting a decrease in protein synthesis, autophagy and inhibited cell growth. FKBP12 is an immunophilin with prolyl isomerase actions. It binds to rapamycin to create the rapamycin-FKBP12 complex that inhibits mTOR [7]. mTORC2 was recently thought to be insensitive to rapamycin. However, recent studies demonstrate that it might be repressed by long-term rapamycin treatment [5].

Rapamycin is otherwise called Sirolimus. It is a macrocyclic lactone that is created by the bacterium Streptomyces hygroscopicus from soil samples in Easter Island. In 1975, S. hygroscopicus was shown to hinder the growth of fungi while having no activity against gram-positive and gram-negative bacteria. It also demonstrated low toxicity in mice. It was first created as an antifungal drug and was found to have immunosuppressive properties [8].

Rapamycin, in 1988, was found to have antirejection properties without the adverse effects found in other antirejection drugs. It was approved by the FDA in 1999 for use in transplant patients as an immunosuppressive agent and an anti-rejection drug. It was likewise found to restrain the growth and development of mammalian cells, thus it has potential as a cancer treatment [9].

Changes in TOR have expanded the lifespan of yeast, Caenorhabditis elegans, and Drosophila [10-12]. Expanded life span could be accomplished by diminished TOR signaling. Rapamycin, which hinders TOR signaling, may expand life expectancy in different species, including mammals.

This study aims to review current evidence on the anti-aging properties of rapamycin.

## Methods

A systematic search for literature was done using PubMed. The keyword "rampamycin aging" was used. The studies were limited to those published in English but the study location can be worldwide. Studies were included if they were about the anti-aging effects of rapamycin. The author narratively described the major findings and conclusions from individual studies. Out of the 79 studies reviewed, only 49 studies fit the criteria

## Results

### Effects on lifespan

The National Institute on Aging Interventions Testing Program was a study chosen by Science as one of the major scientific leaps in 2009. It revealed that giving rapamycin to mice resulted in greater life expectancy, both mean and maximum. It was the first report to demonstrate that a drug could increase the life expectancy of a mammal. Greater life expectancy was seen in both male and female mice heterozygously [13].

The effects of rapamycin on lifespan apply to all mice in general. Increased lifespan was seen when it is given later in life, such as at 19 months of age, which would be equivalent to 65 years old in people [13]. In the other rapamycin studies, rapamycin not only expanded the lifespan of certain strains of normal laboratory mice; it also increased the lifespan of mice models of human diseases. Studies which have compared male and female mice have shown that rapamycin had a greater impact on the lifespan of female mice [14].

Out of 16 studies wherein the life expectancy of rapamycin-treated mice has been examined, two studies that used transgenic mouse models of amyotrophic lateral sclerosis demonstrated no increase in life expectancy [5].

A study also compared the effects of the different doses of rapamycin on the lifespan of male and female UM-HET3 mice. Lifespan was demonstrated to be dose-dependent from one-third to more than three times the concentration. The effects of rapamycin on the lifespan of mice occured within a broader dose range. The hypothesis that rapamycin increases mean and maximum lifespan in mice firmly recommends that rapamycin increases life expectancy by slowing down aging. While rapamycin improves physiological capacity that decreases in older age, other functions are not modified by rapamycin [15].

The effects of rapamycin on end-of-life pathology were likewise examined and included the reasons for death. In two separate studies utilizing genetically heterogenous mice, there was no change in the reason for death. There was no distinction in most end-of-life pathology or cause for death in male and female C57BL/6 mice, aside from a decreased number of neoplastic lesions and adenomas in female mice who were given rapamycin. Expanded lifespan was related to little change in end-of-life pathology. Rapamycin (or rapalogs) not just decreases the growth and spread of tumors, it likewise expands the lifespan of mice [16].

The effects of rapamycin on the age-related diseases were studied through mice which were given rapamycin. These mice lived three to four months longer (similar to 10 years in human years) yet had similar health conditions and quality of life at time of death as mice who didn't consume rapamycin. Mice which consumed rapamycin showed improvement in function and in some physiological parameters and had decreased incidence or severity of some age-related diseases [17].

Weekly treatment with rapamycin prevented the decline and death of male mice who were fed a high-fat diet. All mice treated with rapamycin survived, while 60% of control mice on a high-fat diet developed morbidity or died. Survival was accomplished by intermittent injections of rapamycin, with significant effects in those treated once every week [18].

In a subsequent report that studied subjects starting at 9 months of age, rapamycin increased longevity in males and females by 10% and 18%, respectively, and maximum lifespan by 16% and 13% respectively. Rapamycin was microencapsulated in an enteric covering that made it available orally, and blood levels were three times higher than the regular therapeutic range for immunosuppression in people [19].

Rapamycin increased lifespan (mean lifespan of the last 10% survivors) in a strain of mice with tumors (FVB/N HER-2/neu transgenic). It likewise increased longevity in 129/Sv mice with a typical lifespan and tumor occurrence rate. Around 22.9% of the treated mice were alive after the last control animal died [20].

## Cognition

Good cognition leads to good quality of life in humans. Rapamycin improves learning, memory, and performance in old mice. It reestablishes memory in transgenic mouse models of Alzheimer's disease. Rapamycin strongly affects cognitive performance in mice. It decreased plaques and tangles in mice who were fed rapamycin for 16 months versus control [21].

This large study of the impact of rapamycin on around 150 aging phenotypes in 25 various tissues of male C57BL/6 mice distinguished some aging phenotypes that were improved by rapamycin. These phenotypes were behavior/cognition, immune function, and pathological lesions [22].

## Motor function

Rapamycin was found to improve motor function in models of Huntington disease and Parkinson's disease. The impact of Rapamycin on muscle function was also studied, and rotarod performance was studied. Rotarod is a measurement of muscle function, balance, and coordination. Rotarod performance and walking improved altogether in old male and female mice after rapamycin treatment. There was improved rotarod performance in mice with muscle dystrophy and Huntington disease. Rapamycin decreased stiffening and loss of flexibility in the tendons of old mice [23].

## Cardiovascular system

Neff., *et al.* found that vision, hearing, and heart and skeletal muscle function were not changed by rapamycin treatment, which were all essential to quality of life. However, rapamycin was shown to improve heart function in old mice and in Lmna–/– mice [24]. Rapamycin also decreased atherosclerotic plaques in mouse models of atherosclerosis.

## Other effects

Rapamycin pulse treatment can improve stem cell function and can enhance wound healing. Transient treatment with rapamycin was able to preserve stem cell function. Rapamycin can improve and even boost immune response [25].

Histopathologic examination was done on mice treated with Rapamycin. It was found that precancerous lesions were markedly diminished, while other age-related lesions such as cataracts were not changed [24]. Rapamycin also decreased various histopathology endpoints in the heart, liver, adrenal organs, and endometrium in old mice, however, there was increased cataract formation [23].

## Anti-Cancer effects

Rapamycin and rapalogs are able to crosslink the immunophilin FK506 binding protein, tacrolimus or FKBP-12, with its methoxy group. The rapamycin-FKBP12 complex competes with the FRB domain of mTOR. Molecular association between FKBP12, mTOR, and rapamycin can keep going for around three days (72 hours). The inhibition of mTOR obstructs the binding of the accessory protein raptor (regulatory-associated protein of mTOR) to mTOR, yet that is fundamental for downstream phosphorylation of S6K1 and

4EBP1. As a result, S6K1 dephosphorylates, which lessens protein creation and diminishes cell movement and size. Rapamycin instigates dephosphorylation of 4EBP1 also, bringing about an expansion in p27 and a reduction in cyclin D1 expression. This prompts late blockage of G1/S cell cycle. Rapamycin has appeared to prompt cancer cell deaths by activating autophagy or apoptosis, however, the molecular mechanism of apoptosis in cancer cells has not yet been completely known. One theory to the connection between mTOR blockage and apoptosis may be through the downstream target S6K1, which can phosphorylate BAD, a pro-apoptotic molecule, on Ser136. That response breaks the attachment of BAD to BCL-XL and BCL2, which are mitochondrial death inhibitors, bringing about inactivation of BAD and diminished cell survival. Rapamycin has additionally appeared to instigate p53-free apoptosis in specific types of cancers [26].

**Figure 2:** The effects of rapamycin and rapalogs on cancer. Lybbar12 [CC BY-SA 3.0 (https://creativecommons.org/licenses/by-sa/3.0)].

To delay the development of cancers and expand longevity in p53+/− mice, treatment with rapamycin should be started early in life before tumors form. Rapamycin may be less effective when cancer has grown. Caloric restriction was able to delay cancer in p53−/− mice [27].

## Rapamycin as monotherapy

Rapalogs have improved pharmacokinetics yet have not fared well in human aging trials. They are currently approved for the treatment of renal cell carcinoma (temsirolimus and everolimus) and for patients with pancreatic cancer or tuberous sclerosis. They act by inhibiting mTORC1, prompting an increase in PI3K and AKT signaling by averting negative feedback through S6K and GRB10. AKT action might be modified by ensuing mTORC2 disturbances during long-term treatment which, if not adequately controlled, can progress to cancers [28]. Examples of rapamycin derivatives, otherwise known as rapalogs are temsirolimus, everolimus, ridaforolimus, 32-deoxo-rapamycin and zotarolimus [29].

When utilized as a single treatment, rapamycin and rapalogs may not have immunosuppressive effects in people or mice. Patients who were treated with rapalogs experienced no changes in quality of life nor side effects. The toxicity profile of rapamycin is well-established and its use is safe even when used for a long time in patients at high risk for certain diseases [30].

Studies are currently being done to further test the efficacy of rapalogs in cancers, especially among kidney cancer and breast cancer patients. Current data shows that it is feasible to study rapamycin's effects in age-related diseases, especially the debilitating ones with no known treatment at present, such as Alzheimer's infection and other neurodegenerative diseases [31].

## Possible adverse events

Until this time, no physiological function that changes with age is negatively affected by rapamycin. Few studies in the past have proposed that rapamycin may negatively affect memory, such as decreased long-term memory and solidification and long-term brain plasticity [22].

Regarding rapamycin toxicities, studies have shown vague outcomes. Common findings were nephrotoxicity and testicular degeneration. There was no proof of kidney disease progression at end of life in either male or female mice which were fed with rapamycin. Thus, the main toxicity seen in mice who were fed rapamycin long-term was testicular degeneration [32].

Rapamycin, when given in high, long-term doses, doesn't bring about significant side effects; in fact, rapamycin was able to increase longevity in all animal studies. Rather than daily treatment, rapamycin can be utilized in intermittent intervals [33].

In organ transplant patients, rapamycin and evirolimus are given in high dosages every day to accomplish steady and full inhibition of mTOR complex 1 (mTORC1). In preventing age-related diseases, full treatment may not be necessary [34].

Rapamycin toxicities and symptoms are best observed in clinical trials involving cancer patients where rapalogs are utilized as a monotherapy. Mammalian target of rapamycin (mTOR) inhibitors has consistent and specific toxicities such as hyperlipidemia, hyperglycemia, stomatitis, rash, and myelosuppression, which are not serious. Interstitial pneumonitis is a rare potential serious toxicity that resolves after discontinuing treatment [17].

The possible adverse reactions include a suppressed immune system. A carefully controlled trial on the utilization of rapamycin in renal transplant patients found that 34% of patients had viral infections, while 16% had fungal infections [35].

In renal transplant patients, there is edema in about 60% of patients and aphthous ulcers in about 55% of patients. There may also be mucositis and rash and hair and nail problems, with 90% of patients having alopecia [35].

Side effects concerning the reproductive system include loss of testicular function and diminished male fertility in humans and mice [36].

Metabolic adverse reactions include hyperlipidemia, diminished insulin sensitivity, glucose intolerance and increased occurrence of new diabetes [37].

Other adverse events are gastrointestinal problems such as diarrhea (with long-term use), anemia, renal toxicity, slow wound healing, and joint pains [38].

### Half-Life and Clearance

Rapamycin clearance occurs at a faster rate in mice than in people. Levels of rapamycin in mice drop 20-fold the following day after infusion. In humans, its terminal half-life is around 2.5 days. A 1.5 mg/kg infusion in mice is deemed equivalent to the therapeutic oral dose in humans [39].

As of now, rapamycin is given daily at centers in a high dose. In many animal studies, rapamycin was additionally utilized as daily treatment orally or by infusion which can enhance longevity. Rapamycin may be given every other day and even weekly or twice-a-week with no problems [40].

Two groups of mice who were fed a high-fat diet had 3 i.p. infusions of 1.5 mg $kg^{-1}$ or 0.5 mg $kg^{-1}$ of rapamycin in one week, followed by a rest period. Weekly treatment with one infusion of 1.5 mg $kg^{-1}$ of rapamycin was done, which had superior effects [18].

## Discussion

Direct mTOR inhibitors are promising compounds that inhibit both mTORC1 and mTORC2. These include torin 1 and WYE-125132, which are dual PI3K/mTOR kinase inhibitors with essential yet vague activities, including rapamycin-resistant activities of mTORC1. Though, as these compounds unequivocally repress both mTORC1 and mTORC2, it is improbable that they will have less undesirable reactions than rapamycin [41].

There are many mechanisms behind the lifespan extension effects of rapamycin. Rapamycin has anti-cancer effects which may be due to tumor suppression, which is not related to aging. However, it should also be noted that primary studies about rapamycin and the role of mTOR in longevity were done in postmitotic organisms such as flies and worms or single-celled organisms such as yeast, which do not experience cancers [7].

Secondly, rapamycin expands life span maximally, thus slowing down the progression of many age-related diseases.

Thirdly, rapamycin is able to delay various age-related changes in mice, including the loss of stem cell functioning, cognitive decline, retinopathy, accumulative changes in the myocardium, liver damage, endometrial hyperplasia, tendon stiffening, and decrease in physical movements [7].

The other mechanism is translation. mTORC1, through S6K and 4E-BP, assumes a major role in translation regulation. Diminishing rate of translation may decrease stress on the processes that lead to incorrect, misfolded, or damaged proteins. There may be increased longevity because of deletion or siRNA-mediated knockdown of ribosomal subunits, S6K, or translation factors in S. cerevisiae, C. elegans, and D. melanogaster [42].

Increased longevity may be due to S6K1 deletion in female mice. However, while female mice that lack S6K1 have increased lifespans, there is no recognizable impact on translation in general, even in skeletal muscle. 4E-BP deletion hinders the life-expanding impacts of caloric restriction in flies [43].

Translation is not only the process involved, since longevity extension because of translation initiation factor deletion depends on daf-16, while longevity extension by TOR, S6K, or ribosomal subunits depletion does not. Decreasing TOR by using RNAi fails to further increase the lifespans of eat-2 worms, which are models for caloric restriction, while the low rate of protein synthesis is further

suppressed by 49%. Inactivation of the worm homolog of AMPK is adequate to diminish longevity in animals which lack S6K, apparently without affecting translation [44].

The other mechanism is through autophagy, in which cells reuse their proteins and organelles. It enables cells to survive conditions with limited nutrients and is also an important mechanism that removes damaged cell parts. If there are enough nutrients, mTOR phosphorylates and restrains the autophagy-starting kinase ULK1. The inactivation of genes that are engaged with autophagy diminishes longevity in yeast, C. elegans, and Drosophila. On the other hand, autophagy in the fly sensory system expands longevity [45].

Autophagy is required for the augmentation of longevity in yeasts and longevity through caloric restriction or genetic inhibition of mTOR signaling in worms. This process assumes a critical role in the aging process of mammals. It revives liver tissue and the capacity of aged mice. It has beneficial impacts on the heart, liver, and kidneys. Rapamycin promotes nuclear blebbing and premature senescence in cells from patients with Hutchinson-Gilford progeria, an uncommon premature aging disorder [46].

Progeria results from the misspliced variation of lamin A, also known as progerin, that collects in patients and is likewise identified in smaller amounts during normal cell aging. Rapamycin seems to promote the clearance of progerin from damaged cells by autophagy and limits the accumulation of progerin due to aging [47].

Another mechanism is through the maintenance of stem cells. Rapamycin treatment can reestablish the capacity of stem cells to renew in mice who are exposed to high oxidative stress and who have decreased functional capacities [48].

The activity of mTORC1 is raised in stem cells from aged mice, which show functional deficits from Tsc1 deletion. (Chen., *et al*). There is reestablished functional capacities in stem cells from aged mice and there is boosted immune response to influenza virus infection. There is increase in the self-renewal of intestinal stem cells by inhibiting mTORC1 in the adjacent Paneth cells [49].

Rapamycin improves the reprogramming of body cells to induce pluripotent stem cells, thus promoting stem cell function. It weakens pluripotency, diminishes proliferation, and allows differentiation in human embryonic stem cells. It removes leukemia-initiating cells and represses renewal and differentiation of stem cells from infantile hemangioma, thus protecting against cancer stem cells [50].

Rapamycin also leads to increased longevity through its anti-inflammatory effects. Long term, low-grade inflammation can lead to aging and every chronic disease has inflammation. Rapamycin has both positive and negative impacts on intrinsic and adaptive immunity, with a net result that is more complicated than basic immunosuppression, based on its capacity to improve the immunity of old mice against influenza virus [51].

While rapamycin has a high specificity for mTORC1 during acute treatment, long-term exposure can likewise hinder mTORC2. Data obtained from studies concerning C. elegans propose that the inhibition of mTORC2 can likewise increase lifespan. Increased longevity by the disruption of mTORC1 in worms requires skn-1 (which is the homolog of mammalian NRF1/2) and daf-16 (which is the homolog of mammalian FOXOs), which are both transcription factors that control the genes that protect against stress [52].

There is likewise an association between TOR and endocannabinoid signaling. Small particles similar to a mammalian endocannabinoid were found in C. elegans, and the depletion of these molecules was related to increased longevity by caloric restriction. A certain molecule, eicosapentaenoyl ethanolamide (EPEA), was likewise observed to be lower in worms that lack S6K, and treatment with EPEA decreased longevity in the two models while enabling high susceptibility to heat stress [53].

## Conclusion

To conclude, rapamycin demonstrates significant promise in animal models as a drug for the treatment of age-related diseases. However, the significant reactions limit its long-term use in people. Further research will be required to know if rapamycin will be helpful to human lifespan and protect against age-related diseases.

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