ABSTRACT

"Rapamycin vs Metformin: A Comparative Anti-Aging Study"

Dr. G. Ushakiran *, M. Naga Nandini[1], N. Swathi[1], Sd. Afreen[1], U.Veda sai manogna[1] ,Y. Sri pujitha[1].

* Corresponding author, Professor, NRI College of pharmacy, Pothavarappadu-521212.

1 IV B.Pharmacy students, NRI college of pharmacy, Pothavarappadu-521212.

Corresponding author:

Dr.G.Usha kiran

Anti-aging therapies aim to promote longevity and delay age-related diseases. Two promising candidates are rapamycin and metformin. This comparative study investigates their molecular mechanisms, efficacy, and safety. Rapamycin (mTOR inhibitor) reduces oxidative stress, improves cellular senescence, and enhances autophagy. Metformin (AMPK activator) improves insulin sensitivity, reduces inflammation, and promotes cellular stress resistance. While both drugs show anti-aging potential, rapamycin excels in cancer prevention and cognitive function, whereas metformin improves cardiovascular health and reduces metabolic disorders. This study highlights the need for personalized treatment strategies and further research to optimize anti-aging therapies.

KEYWORDS : Anti aging , rapamycin, metformin ,

ABBREVIATIONS:

AMPK: 5'adenosine monophosphate-activated protein kinase

mTOR: Mammalian target of rapamycin

ULK1: Unc-51-like kinase 1

FOXO: Forkhead box O

ATG13: Autophagy-related protein 13

NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells

DNMT3B: DNA methyltransferase 3beta

INTRODUCTION:

Ageing is a complex process involving numerous mechanisms that can lead to damage and decrease in both the body's external and internal functions. At the cellular level, this can cause organ damage, leading to reduced skin elasticity, an increased risk of developing neoplasms, decreased endurance and strength, osteoporosis, and various other conditions. If we consider it in medicine, it is the accumulation of a wide range of cellular and molecular damage over time **(1).**

Behavioral, dietary, and pharmacological approaches have been proposed as potential strategies for promoting healthy aging and increasing lifespan. These approaches focus on modifying lifestyle factors, such as physical activity, stress management, and sleep, as well as dietary habits, like caloric restriction and plant-based diets **(2,3).** Additionally, certain pharmacological interventions, including hormone replacement therapy, metformin, and senolytics, have been explored for their potential anti-aging effects **(4,5).**

This article will provide an overview of the current state of anti-aging medicine, including the latest research and evidence on behavioral, dietary, and pharmacological approaches. We will examine the potential benefits and limitations of these strategies and discuss the future directions of anti-aging research.

One of the key areas of focus in anti-aging medicine is the role of cellular senescence in the aging process. Senescent cells are cells that have reached the end of their lifespan and are no longer able to divide **(6).** These cells can accumulate over time and contribute to the development of age-related diseases. Senolytic therapy, which targets and eliminates senescent cells, has shown promise as a potential anti-aging intervention **(7).**

Another important area of research is the impact of diet on aging. Caloric restriction, in particular, has been shown to have anti-aging effects in animal models **(8),**and some studies suggest that it may also have benefits for human health **(9).** Additionally, certain nutrients, such as omega-3 fatty acids and antioxidants, may help to promote healthy aging by reducing inflammation and oxidative stress **(10).**

Finally, there is growing interest in the potential role of pharmacological interventions in anti-aging medicine. Metformin, a drug commonly used to treat type 2 diabetes, has been shown to have anti-aging effects in animal models **(11),** and some studies suggest that it may also have benefits for human health **(12).** Other potential anti-aging drugs, such as rapamycin and NAD+ boosters, are also being explored. **(13, 14)**

This study/article aims to investigate the anti-aging effects of rapamycin and metformin, exploring their molecular mechanisms, efficacy, and safety profiles, with the goal of identifying potential therapeutic strategies for promoting healthy aging and preventing age-related diseases.

SYMPTOMS OF AGEING:

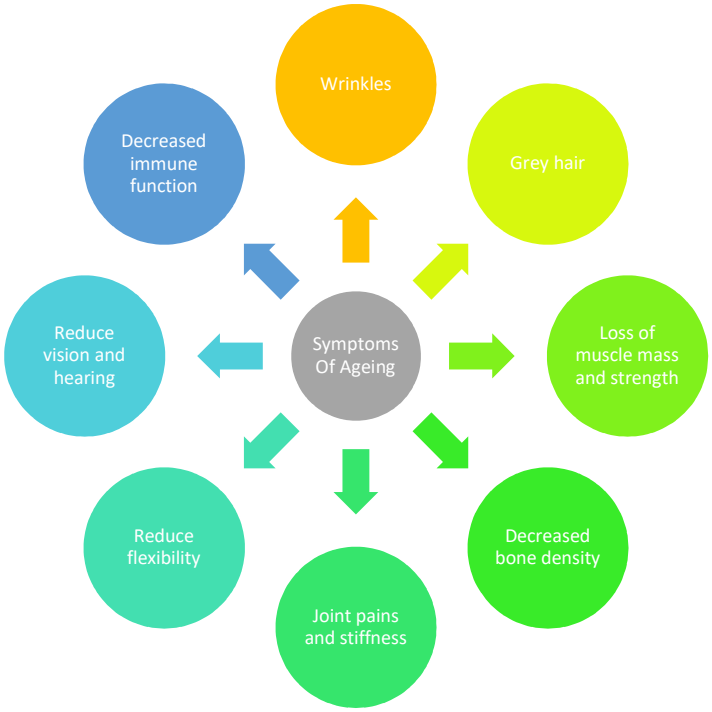

Fig: Symptoms of ageing

ADVANTAGES OF ANTI AGEING DRUGS (15):

Anti-Ageing Drugs have several benefits, including:

-Preventing organ transplant rejection by suppressing the immune system

- Treating certain types of cancer by inhibiting cell growth

- Preventing cardiovascular diseases by coating heart stents

- Reducing the risk of CMV infection during organ transplantation

- Enhancing antipathogen and anticancer immunity in mice

- Inhibiting viral replication

- Slowing down aging and increasing lifespan, which is a major focus for young adults

- Promoting overall better health

DISADVANTAGES OF ANTI AGEING DRUGS(15) :

Nevertheless, it is important to take into account some disadvantages as well:

-Side effects like diarrhea, nausea, stomach pain, and headache

- Long-term use of Metformin can lead to vitamin B12 deficiency and anemia

- Interactions with other medications like thyroid and diuretics

- High doses of Rapamycin can decrease blood cell count, leading to reversible thrombocytopenia, anemia, and leukopenia

-High concentrations can cause dry skin and peeling.

TYPES OF AGEING (16):

Intrinsic aging is characterized by:

- Reduced collagen production

- Decreased blood supply

- Loss of skin fat

- Loss of rete ridges, which connect the epidermis and dermis

This results in:

- Dry, pale skin

- Wrinkles

- Less elastic skin

- Slower skin renewal (keratosis)

Extrinsic ageing, on the other hand, is caused by external factors and manifests as:

- Rough wrinkles

- Hyperpigmentation (age spots) or hypopigmentation (skin lightening)

- Actinic keratosis (precancerous skin lesions)

PATHOPYSIOLOGY OF AGEING:

Three different pathways can reasonably explain the pathophysiology of ageing:

Generation of Free Radicals

Free radicals are well known in the biochemical world as a typical result of good physiology in well-controlled, tiny numbers. They exist as a molecule with a single, unpaired valence electron, making them highly reactive in the presence of other substances as they try to interact with them to gain more valence electrons and balance the electron configuration. The precise mechanisms underlying the downstream negative effects of free radical generation and subsequent interaction with cellular components are beyond the scope of this paper, but it is worth noting that free radicals can denature proteins, destroy membrane lipids, nucleic acids, and certain organelles such as lysosomes and proteasomes.[19] Understanding free radical or reactive oxygen species-derived degenerative changes is important because it is believed that accumulated cellular damage caused by these molecules will eventually overwhelm the cell's damage repair mechanisms, resulting in the physiologic collapse of first the cell, then the entire organism.

Glycation

When aldehyde groups in reducing sugars react with amino groups in proteins, advanced glycosylation end products are formed. The synthesis of these metabolic products is dependent on high blood glucose.[20] Glycemic regulation weakens with age, and glucose tolerance can

change significantly. The presence of advanced glycosylation end-products can cause problems such as vascular fibrosis, thicker basement membranes, poor lipid metabolism, and diminished collagenous flexibility. Furthermore, advanced glycosylation end-products are linked to the activation of inflammatory responses, resulting in the production of inflammatory chemicals and reactive oxygen species, which causes additional tissue damage.

Reduced Regenerative Capacity

In healthy people, there is a balance between one cell's apoptosis and the maturation and healthy growth of another cell that effectively replaces the first. Researchers believe that systems within the cell cycle manage a senescent cell's programmed demise while simultaneously signaling to other cells that a fresh, healthy cell is needed to match whatever metabolic demands the senescent cell may have been meeting. The course of the cell cycle is controlled by regulatory proteins, which function significantly less in senescent cells than in younger, healthy cells. These protein-derived signaling pathways appear to have a diminished ability to communicate the need for cell regeneration and maturation in healthy, youthful cells. **(17-19)**

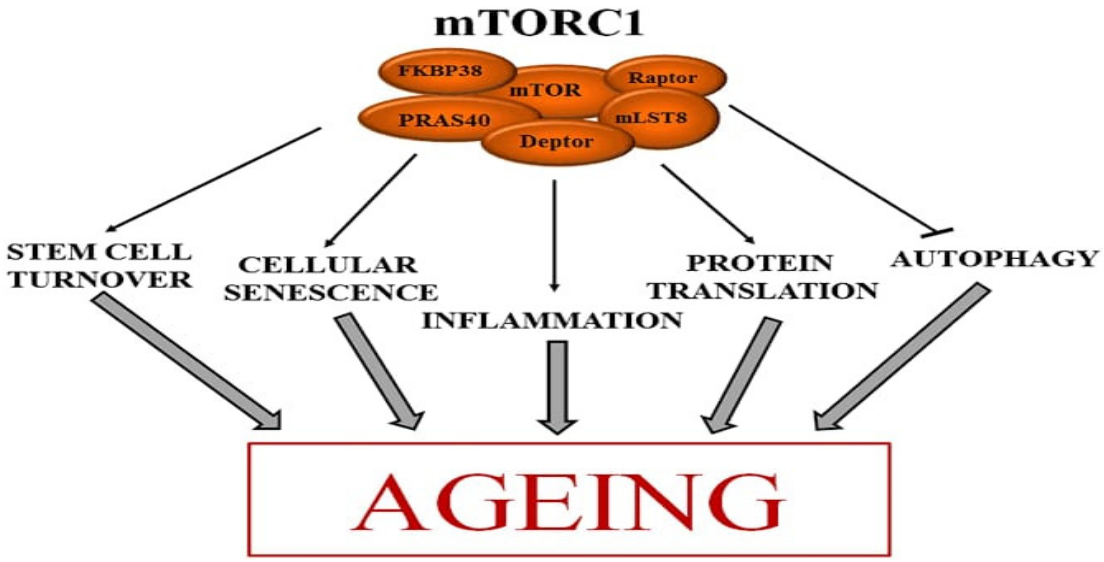

Fig: Pathophysiology of ageing

ANTI-AGEING DRUGS:

METFORMIN:

Metformin, also known as N, N-dimethyl biguanide, is a hypoglycemic medication with two connected guanidine rings. It originated from the therapeutic herb Galega officinalis, often known as French lilac.

In 1653, Galega officinalis was originally described in Culpeper's Complete Herbal as a remedy for worms, fever, pestilence, and epilepsy.

- 1772: John Hill advocated Galega officinalis for the treatment of diabetes.

- 1957: French physician Jean Sterne described metformin's antihyperglycemic characteristics and its use to treat diabetes.

Metformin became popular in Europe for diabetes therapy, but experienced difficulties in the US due to worries about lactic acidosis**.**

- 1995: Metformin was demonstrated efficacious and safe, resulting in its adoption in the United States.

Current Status: Metformin is the first-line treatment for type 2 diabetes**.(20)**

MECHANISM ACTION OF METFORMIN:

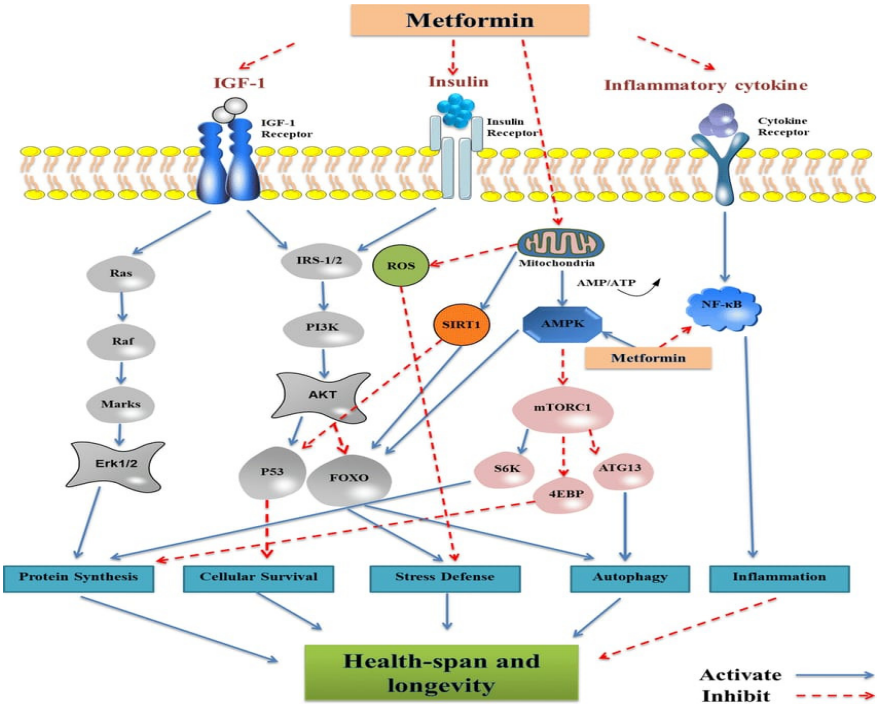

Fig: Mechanism of action of Metformin

AMPK is an upstream regulator of the mTOR signaling pathway. Numerous studies have shown that the AMPK signaling pathway's activating capacity declines with age, disrupting autophagy, increasing cellular stress, and promoting inflammation, all of which contribute to the development of many age-related diseases, including cardiovascular disease, diabetes, and cancer. Similarly, enhanced activation of the AMPK system has been demonstrated to lengthen lifespan in lower organisms in response to CR and pharmacological treatments such as metformin. Activated AMPK phosphorylates and activates ULK1 of the ULK complex, promoting autophagy.

It also activates the FOXO transcription factors, which transactivate genes involved in detoxification, autophagy, cancer suppression, and energy balance. AMPK activation reduces aging by suppressing NF-κB, a key regulator of immunity. It also reduces ER stress and oxidative stress by increasing the production of mitochondrial uncoupling protein (UCP-2). Metformin changes global methylomes through the H19/SAHH axis. H19, a long noncoding RNA that should be downregulated in adults, disrupts the methylation profile by binding to and blocking s-adenosylhomocysteine hydrolase (SAHH), which typically hydrolyzes SAH and

eliminates its inhibition of DNMT3B. Metformin stimulates AMPK and upregulates let-7, a microRNA family that targets and degrades H19. **(21)**

SIDE EFFECTS OF METFORMIN(22):

1. Gastrointestinal issues:
   - Diarrhea , abdominal pain.
   - Nausea , vomiting.
2. Vitamin B12 deficiency:
   - Fatigue , weakness.
   - Shortness of breath , dizziness.
3. Lactic acidosis (rare but serious):
   - Muscle pain , weakness, fatigue.
   - Shortness of breath
   - Abdominal pain
4. Hypoglycemia (low blood sugar):
   - Shakiness , dizziness.
   - Sweating , confusion, headache.
5. Other possible side effects:
   - Headache , fatigue.
   - Weight loss
   - Muscle pain , joint pain.

RAPAMYCIN:

Rapamycin is also known by the trade names sirolimus or rapamun.

Discovered and produced by Streptomyces hygroscopicus.

- Discovery Location: Easter Island.

- Discovered by Georges Nogrady in the late 1960s.

- Initial interest in antifungal properties. - Scientific development. - Discovery by scientists at Ayerst Pharmaceuticals, Canada.

- Naming: Rapamycin was named after the antifungal chemical found in the bacteria.

- Research Focus: After being discovered to limit eukaryotic cell proliferation, it was shifted from antifungal to immunosuppressive and anticancer.

Medical Use: - FDA Approved in 1994. - Initially used to prevent organ rejection in liver transplant patients.

- Trade names: Sirolimus and Rapamune.Recent findings include: Lifespan Extension. In 2009, it was reported that both male and female mice lived longer lives. **(23)**

MECHANISM ACTION OF RAPAMYCIN:

Rapamycin and metformin target the mTOR and 5'-AMP-activated protein kinase, respectively . The mTOR consists of two complexes, mTORC1 and mTORC2, which coordinate a wide range of cellular metabolic processes related to production, growth, and somatic maintenance, including protein synthesis, mitochondrial function, and cell proliferation. Activated mTORC1 promotes mRNA translation and protein synthesis in the cell by phosphorylating the p70 ribosomal protein S6 kinase (S6K) and the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). It also inhibits autophagy by phosphorylating ULK1, ULK2, and ATG13 of the ULK complex, as well as the transcription factor EB, both of which are required for autophagy. Not unexpectedly, a growing body of research has found that unregulated mTOR signaling is linked to the aging process and the advancement of age-related diseases including cancer and diabetes. Rapamycin inhibits mTOR signaling by first attaching to the immunophilin FK binding protein (FKBP12) and then targeting mTORC1 and mTORC2(23).

While reducing mTORC1 increases life expectancy and protects against age-related disorders, inhibiting mTORC2 has unintended consequences, including glucose intolerance and altered lipid profiles. Nevertheless, mTORC2 is less susceptible to rapamycin, and its suppression requires long-term treatment.

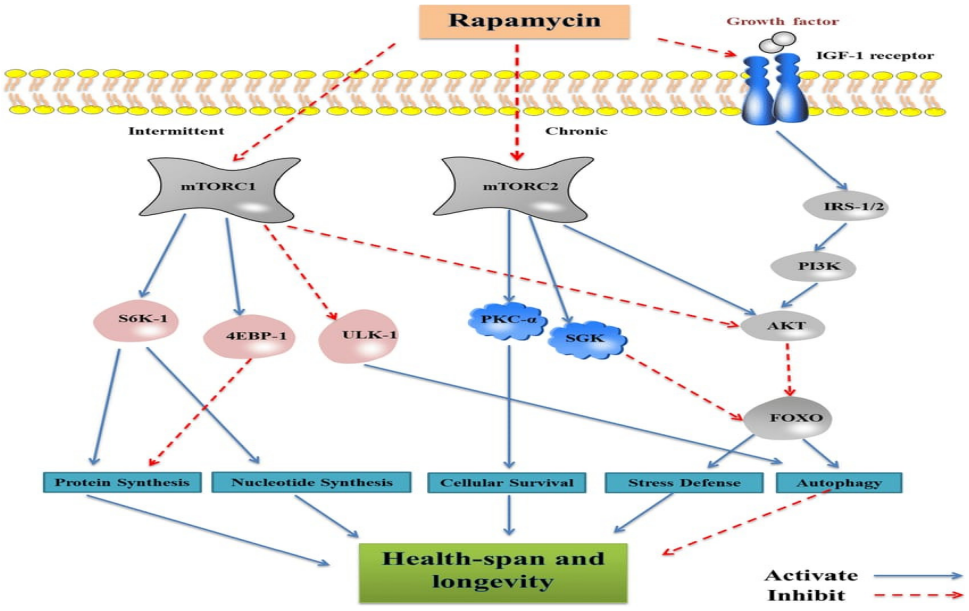

Fig: Mechanism of action of rapamycin

SIDE EFFECTS OF RAPAMYCIN(24):

1. Immune system suppression:
   - Increased risk of infections
   - Reduced immune response
2. Metabolic changes:
   - Hyperlipidemia (elevated cholesterol and triglycerides)
   - Hyperglycemia (elevated blood sugar)
   - Insulin resistance
3. Kidney function impairment:
   - Reduced kidney function
   - Increased creatinine levels
4. Hormonal changes:
   - Testosterone reduction
   - Thyroid hormone changes
5. Gastrointestinal issues:
   - Diarrhea , Nausea .
   - Vomiting , Abdominal pain.
6. Musculoskeletal problems:
   - Muscle weakness , joint pain , osteoporosis.
7. Dermatological issues:
   - Skin rash , acne , hair loss.
8. Neurological effects:
   - Headache ,mood changes .
   - Memory impairment
9. Other possible side effects:
   - Anemia
   - Thrombocytopenia (low platelet count)
   - Leukopenia (low white blood cell count)

COMPARATIVE STUDIES:

Metformin and rapamycin have distinct mechanisms of action and anti-aging effects. Metformin activates AMPK, improving glucose metabolism, reducing oxidative stress, and increasing lifespan up to 10% in mice, with potential benefits for cardiovascular health. In contrast, rapamycin inhibits the mTOR pathway, improving cellular senescence, reducing cancer incidence, and increasing lifespan up to 20% in mice, with additional benefits for immune function and age-related decline in physical and cognitive function. While both drugs have anti-aging properties, rapamycin's effects are more comprehensive and pronounced. Combination therapy may have synergistic effects, with metformin enhancing rapamycin's effects on autophagy and cellular senescence, and rapamycin enhancing metformin's effects on glucose metabolism and insulin sensitivity.

However, rapamycin's immunosuppressive effects and increased risk of infections and hyperlipidemia must be considered, whereas metformin is generally well-tolerated. Ultimately, rapamycin's more potent anti-aging effects make it a more effective choice for anti-aging purposes, but further research is necessary to confirm these findings in humans **(24 -27).**

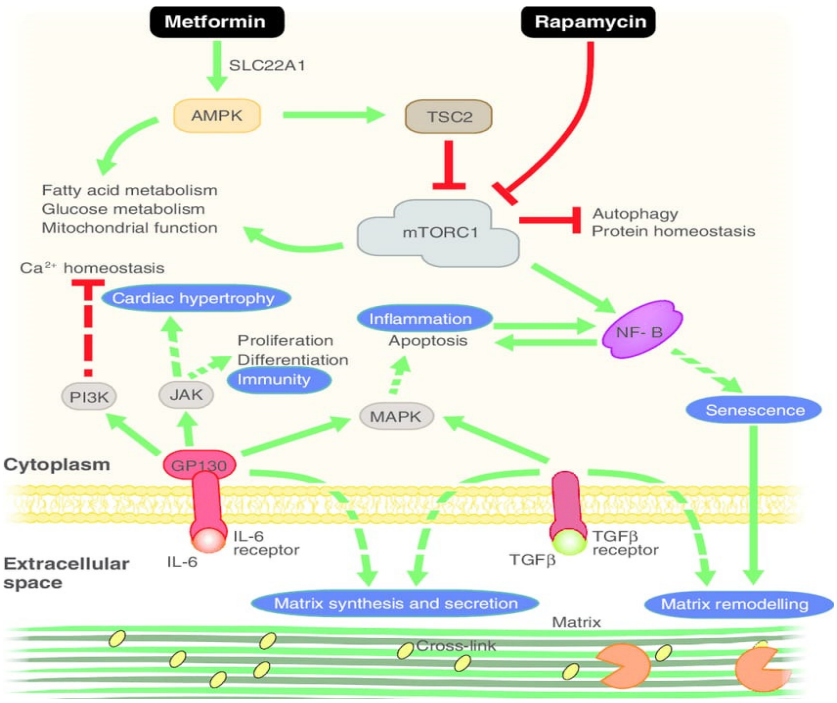

Fig: Comparison of mechanism of action between metformin and Rapamycin

CONCLUSION:

Rapamycin appears to be more effective in producing anti-ageing activity compared to metformin. While both drugs have anti-ageing properties, rapamycin's effects on cellular senescence, autophagy, and immune function make it a more potent anti-ageing agent. Rapamycin has consistently shown to increase lifespan in animal models, with up to 20% increase in mice, and improves age-related decline in physical function and cognitive function. In contrast, metformin's anti-aging effects are less pronounced, with up to 10% increase in lifespan in mice, and primarily focuses on improving glucose metabolism and reducing oxidative stress. Although both drugs have different mechanisms of action and may have synergistic effects when combined, rapamycin's overall anti-aging effects are more comprehensive and pronounced, making it a more effective choice for anti-ageing purposes. However, further research is necessary to confirm these findings in humans and determine optimal dosage and duration of treatment.

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