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Published by Intisari Sains Medis

## Mechanism of action of metformin as an anti-aging agent: a literature review



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Received: 2021-04-12

Accepted: 2021-07-02

Published: 2021-07-14

### ABSTRACT

Aging is a complex process consisting of various mechanisms that can cause damage and decrease the body's extrinsic and intrinsic functions. Metformin has been indicated for the treatment of degenerative diseases. It also has been reported to be used as an anti-aging agent. Various studies reported different mechanisms of action, but human studies are limited. This literature aims to review the multiple mechanisms of action of metformin as an anti-aging agent. Metformin has been reported to exert anti-aging effects by prolonging life in humans and animals. The effectiveness of metformin as an anti-aging agent

is influenced by the dosage and age of the subjects studied. Various mechanisms of action of metformin concerning anti-aging have been reported, including autophagy pathways with AMPK activation and inhibition of mTOR, increased antioxidants, inhibition of ROS, inhibition or enhancement of mitochondrial function and inhibition of inflammation. It was found that there were biomarkers in the form of GPx7, Nrf2, PPAR and SREBP, SOD2, TrxR1, NQO1, NQO2, pNF-kB, FOXO, mTOR, AMPK, which could be used as predictors to explain the anti-aging effect of metformin.

**Keywords:** anti-aging, mechanism of action, metformin.

**Cite This Article:** Hamudin, A., Atik, N. 2021. Mechanism of action of metformin as an anti-aging agent: a literature review. *Intisari Sains Medis* 12(2): 453-458. DOI: [10.15562/ism.v12i2.1058](https://doi.org/10.15562/ism.v12i2.1058)

### INTRODUCTION

Aging is a complex process associated with accumulated damage and loss of bodily functions and increased susceptibility to disease, which in turn leads to death.<sup>1</sup> The evolutionary theory of aging assumes a linear increase in mutations in the protein translation system from time to time continuously so that proteins cannot be translated effectively, which in turn results in aging. At the cellular level, this can lead to organ damage, resulting in decreased elasticity of the skin, a tendency to develop neoplasm, reduced endurance and strength, osteoporosis, and many other conditions. Furthermore, this can lead to a geriatric syndrome, in which there are high falls, frailty, delirium, and falls.<sup>2</sup>

Aging and degenerative diseases are one of the biggest challenges today. This is because aging and degenerative diseases can reduce the quality of life, and the need for various therapies to reduce aging and degenerative diseases can increase the economic burden of the country, including both in developed and

developing countries.<sup>3</sup>

Metformin is a biguanide agent indicated in treating several degenerative diseases such as diabetes mellitus (DM), cardiovascular disease, and cancer.<sup>4-7</sup> In addition, several in vivo and in vitro studies have reported a mechanism of action for metformin extending the life of living things.<sup>8-11</sup> This means that there is potential for metformin as an anti-aging agent. The various studies reported mixed results. Knowledge of the multiple actions of metformin as an anti-aging agent can identify the biomarkers involved in the anti-aging mechanism by metformin. It can be helpful in the development of further clinical research into the potential use of metformin an anti-aging agent in humans. Therefore, this literature aims to review the various mechanisms of action of metformin as an anti-aging agent

### AGING MECHANISMS

Aging consists of intrinsic aging and extrinsic aging. Intrinsic or chronological aging occurs in most body organs, which is part of a degenerative process and

is associated with increasing age.<sup>12,13</sup> Intrinsic aging involves genetic and racial background due to shortening of the telomeres, hormonal changes and increased reactive oxygen species (ROS). Extrinsic aging is caused by external environmental factors, including ultraviolet (UV) rays, pollution, cigarette smoke, chronic disease, and malnutrition.<sup>13</sup>

Aging can occur in all organs of the body, including the skin. In aging skin, a decrease in collagen causes skin rigidity, a reduction in the thickness of the dermis layer by 20 percent and a decrease in other skin physiological functions. Intrinsically aging skin is characterized by a decrease in collagen production, a decrease in blood supply, a decrease in the amount of skin fat, and loss of rete ridges that function as interdigitation or a bond between the epidermis and dermis, so that the results that appear from the outside are like dry, pale skin accompanied by wrinkles. Smooth wrinkles are also less elastic and slow down skin repair.<sup>14</sup> Extrinsically aging skin includes rough wrinkles, hyper or hypopigmentation, actinic keratosis.<sup>13</sup>

Reactive oxygen species plays an important role in the occurrence of aging, both intrinsic and extrinsic. ROS is a molecule that contains oxygen; small, highly reactive and naturally produced in small amounts due to the body's metabolic processes. One form of ROS is free radicals. ROS can react and damage cell components such as lipids, proteins and deoxyribonucleic acid (DNA) when ROS is overproduced. Apart from causing DNA damage, oxidative stress also affects protein translation, providing another aging mechanism through genetic damage.<sup>2</sup> This compound is formed as a natural product of normal oxygen metabolism and has a dual role as a useful and toxic compound.<sup>13,15,16</sup>

The formation of ROS in cells can be done through non-enzymatic and enzymatic reactions. Enzymatic reactions produce free radicals derived from phagocytosis, respiratory chain reactions, cytochrome P-450 enzyme systems and prostaglandin synthesis. Non-enzymatic reactions to form free radicals through reactions between organic compounds and oxygen are initiated by ionizing radiation and occur during oxidative phosphorylation (aerobic respiration) of mitochondria. Sources of free radicals include endogenous sources originating from inflammation, immune cell activation, overactivity, mental stress, cancer, ischemia, aging, infection and exogenous sources that come from cigarette smoke, air pollution, heavy metals, alcohol, food, drugs, certain drugs and injection or absorption through the skin.<sup>15</sup> ROS can be generated intrinsically because cellular metabolism always produces ROS. ROS is also produced by ultraviolet (UV) rays where UV light is the most crucial factor that plays a role in the premature aging of the skin, so it is also called photoaging.<sup>12,13</sup>

## METFORMIN AS A CONVENTIONAL DRUG FOR DIABETES

Metformin is the first-line oral anti-diabetes that is most widely used in the treatment of type 2 diabetes.<sup>17</sup> As a biguanide agent, metformin plays a role in lowering basal and postprandial plasma glucose (PPG). Metformin can be used

as monotherapy, or it can be combined with other antidiabetic agents such as sulfonylureas,  $\alpha$ -glucosidase inhibitors, insulin, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitor and agonists Glucagon Like Peptide-1 (GLP-1).<sup>18</sup>

Metformin works by inhibiting hepatic glucose production, reducing intestinal glucose absorption, utilizing increased peripheral glucose uptake, reducing fasting plasma insulin levels, and increasing insulin sensitivity, reducing blood sugar concentrations without causing hypoglycemia.<sup>3,18</sup> Apart from lowering blood glucose levels, metformin has additional health benefits, lowering total cholesterol levels, lowering low density lipoprotein (LDL) cholesterol levels, increasing high density lipoprotein (HDL) cholesterol levels and preventing several vascular complications.<sup>19</sup> Metformin is also used for other therapy, such as polycystic ovary syndrome (PCOS).<sup>20</sup>

## MOLECULAR MECHANISM OF METFORMIN

Metformin does not cause hypoglycemia in people with type 2 diabetes or normal people, except in the use of metformin in combination with insulin or other drugs that have the effect of lowering blood sugar. Metformin will not cause hyperinsulinemia. Insulin secretion was unchanged with metformin treatment. Metformin treatment can reduce weight.<sup>21,22,23</sup>

Metformin can be an inhibitor of gluconeogenesis by activating the enzyme adenosine monophosphate-activated protein kinase (AMPK). AMPK plays a vital role in regulating energy metabolism, which is a key role in DM and other metabolic-related diseases. AMPK is required to maintain glucose homeostasis. The most common side effects of metformin are gastrointestinal symptoms with an incidence of 20%-30% in vomiting and nausea. The most severe side effect of metformin is lactic acidosis. DM patients with kidney and liver dysfunction, the effect of lactic acidosis occurs with an incidence of 1/3000.<sup>3</sup> In addition to lowering blood glucose levels, metformin also functions as an anti-cancer, anti-aging, neuroprotective agent.<sup>24,25,26</sup>

## PHARMACOKINETICS OF METFORMIN

Food will decrease the absorption rate of metformin. The peak plasma time for metformin preparations is 2-3 hours, while the plasma peak time for long-term release is 4-8 hours. A stable plasma concentration can be assessed for 24 to 48 hours, usually  $<1 \mu\text{g/mL}$ . In clinical trials, if metformin hydrochloride tablets are taken at the maximum dose, the maximum plasma level does not exceed 5 mcg/ml for conventional doses, the maximum effect of metformin may appear in 2 weeks.<sup>24,25,26</sup>

Metformin binding to plasma proteins is minimal or almost absent and can be distributed in red blood cells.

Metformin does not have a first-pass effect on the liver. The renal clearance rate is approximately 3.5 times the creatinine clearance rate. Renal cleansing of about 450-540 mL/minute.<sup>24,25,26</sup>

Ninety percent of metformin occurs in the urine in an unchanged form. In the first 24 hours after oral metformin, approximately 90% of the absorbed drug dose is excreted in the urine. The half-life of the plasma is approximately 6.2 hours. The half-life in the blood is 17.6 hours because the clot of red blood cells can be part of the distribution of the drug.<sup>20,27,21</sup>

## EFFECTS OF METFORMIN ON AGING

The researchers have a different conclusion from the research results that metformin expressed as a potential therapy to slow aging.<sup>28</sup> Research on *Caenorhabditis elegans* with doses of 25, 50 and 100 mM can increase the average lifespan by 18%, 36% and 3%.<sup>10</sup> Similar results reported that studies in mice with metformin doses of 50 mM triggered the greatest prolongation of life compared to other doses.<sup>29</sup> Research on mice, dietary supplementation with metformin 0.1% (w/w) added to food can prolong life up to 5.83%.<sup>8</sup> In a study on male silkworms, low doses of metformin can prolong life by 1.2 days (2.68%).<sup>30</sup>

Different results in the study of male flies, 1 mM metformin supplementation; 2.5 mM; 5 mM; 10 mM; 25 mM and 50 mM did not prolong life and 100 mM metformin supplementation had decreased the lifespan of male flies.<sup>9</sup> The

**Table 1. Some results and mechanisms of action of metformin as an anti-aging agent**

Subject	Dosage	Result	Mechanism
<i>Drosophila melanogaster</i> Slack et al (2012) <sup>9</sup>	0; 5; 10; 25; 50; 100 mM	Does not increase the lifespan of male or female flies	<ul style="list-style-type: none"> <li>- Strong AMPK activation</li> <li>- Reduced lipid stores</li> <li>- Intestinal fluid hemostasis disorders</li> </ul>
Silkworm Song et al. (2015) <sup>30</sup>	0,1 mM	Extend life without losing weight	<ul style="list-style-type: none"> <li>- Increase fasting tolerance</li> <li>- Increase antioxidant glutathione levels</li> <li>- Activates the AMPK signaling pathway, p53 protein, FOXO</li> </ul>
<i>Caenorhabditis elegans</i> Cabreiro et al. (2013) <sup>10</sup>	25; 50; 100 mM	Extends life	<ul style="list-style-type: none"> <li>- Converts microbial folate</li> <li>- Metabolism of methionine</li> </ul>
Espada et al. (2019) <sup>11</sup>	10; 25; 50 mM	Limits survival and shortens old age	<ul style="list-style-type: none"> <li>- worsening of the mitochondrial function associated with aging leading to ATP fatigue</li> <li>- Old cells fail to regulate glycolysis in response to metformin</li> </ul>
Rats male mice Martin-Montalvo et al. (2013) <sup>8</sup>	0.1% w/w	Extends health and lifespan	<ul style="list-style-type: none"> <li>- Induces activation of the Nrf2 target gene</li> <li>- Increase levels of antioxidant protein</li> <li>- Increases stress response, such as SOD2, TrxR1, NQO1 and NQO2</li> <li>- Decrease pNF-kB</li> </ul>
Zhu et al. (2021) <sup>31</sup>	100mg/kg/day	Improve health and prolong life	<ul style="list-style-type: none"> <li>- Increase extracellular matrix related genes</li> <li>- Decreases the expression of genes related to oxidative phosphorylation in the heart</li> </ul>
Human Fang et al. (2018) <sup>32</sup>	100 µm	Extends the life of human diploid fibroblasts and mesenchymal stem cells	<ul style="list-style-type: none"> <li>- Regulates the endoplasmic reticulum GPx7</li> <li>- Increase the accumulation of Nrf2</li> </ul>
Kulkarni et al. (2018) <sup>33</sup>	N.A	Has metabolic and nonmetabolic effects associated with aging	<ul style="list-style-type: none"> <li>- The role of BRCA in DNA damage response</li> <li>- Affects fatty acid metabolism</li> <li>- Affects the biosynthesis of unsaturated fatty acids</li> <li>- Affects PPAR and SREBP signaling</li> <li>- Affects LXR / RXR activation</li> <li>- Affects the trimerization of the collagen chain</li> <li>- Affects ECM remodeling</li> </ul>

results of other studies that contradict the effect of metformin on aging namely on cell survival were carried out by in vitro and in vivo tests with the results that metformin can shorten the life span and limit cell survival when given to old cells as opposed to the neonatal effect in studies with rat. Mechanistically, metformin worsens aging-associated mitochondrial function leading to respiratory failure, exacerbated by adenosine triphosphate (ATP) exhaustion due to the inability of senescent cells to regulate glycolysis in response to metformin. The beneficial dietary restriction effect of metformin on lipid stores is abolished in aged animals, contributing to metabolic failure.<sup>11</sup>

Various studies relating to the effects of metformin on aging have been obtained with different mechanisms of action. In humans, metformin treatment using low doses can prolong the life of diploid fibroblasts and mesenchymal stem cells. Aging human cells have decreased levels of glutathione peroxidase 7 (GPx7) expression. Low levels of GPx7 lead to premature cellular senescence. Nuclear accumulation of nuclear factor-erythroid 2-related factor 2 (Nrf2) is increased in the presence of metformin. Nuclear accumulation of erythroid factor 2 associated nuclear 2-factor 2 (Nrf2) binds to antioxidant response elements in the promoter of the GPx7 gene to

induce its expression.<sup>32</sup> In human studies over 70 years of age, metformin has significant metabolic and non-metabolic associations effects with aging include pyruvate metabolism and repair of deoxyribonucleic acid (DNA) in muscles and peroxisome-proliferator-activated receptor (PPAR) signaling and sterol-regulating element-binding protein (SREBP), oxidation of mitochondrial fatty acids, and trimerization of collagen in adipose.<sup>33</sup>

Several studies report the effects metformin can induce on aging activation of the Nrf2 target gene.<sup>8,33</sup> Metformin also activates the AMPK signaling pathway.<sup>30</sup> The mechanism of action of metformin is

reported to be related to trimerization of collagen chains and to increase the stress response, e.g. superoxide dismutase 2 (SOD2), thioredoxin 1 (TrxR1), quinone oxidoreductase 1 (NQO1) and quinone oxidoreductase 2 (NQO2).<sup>8,34</sup> The unfavorable effects of metformin on aging were related to the age and type of subjects studied and the dosage used. In *C. elegans*, which is aged, metformin can worsen aging-related mitochondrial dysfunction leading to ATP exhaustion and failure of old cells to fail to regulate glycolysis in response to metformin.<sup>11</sup> High doses of metformin given to male flies have a toxic effect that interferes with the hemostasis of intestinal fluid and causes intestinal damage.<sup>9</sup>

## THE MOLECULAR MECHANISM OF METFORMIN AS AN ANTI-AGING

Metformin has a mechanism of action that targets several pathways of aging. The various mechanisms of metformin about anti-aging effects are described as follows:

### Affects mitochondrial function

Studies on *C. elegans* reported that metformin worsened mitochondrial function that causes ATP fatigue in old age so that metformin does not prolong life, but instead shortens life.<sup>11</sup> The mechanism of action of metformin as an anti-aging agent can be carried out by changing the intrinsic function of mitochondria and mitochondrial protein synthesis.<sup>28</sup> This explanation describes the effect of metformin based on the age of the studied subjects. In addition, the effect of metformin as an anti-aging agent is influenced by the dose used this is related to the toxicity effect of metformin.

Research on flies the anti-aging effects of metformin resulted in the use of low doses of metformin, but not at high doses. High doses of metformin cause severe mitochondrial dysfunction that damages cells.<sup>9</sup> Low doses of metformin cause mild mitochondrial dysfunction due to an adaptive hormonal response capable of tolerating toxic agents. In addition, mild mitochondrial dysfunction can induce a low energy state thereby activating AMPK. Both of these mechanisms can lengthen the age.<sup>34</sup>

### Inhibits ROS

At the cellular level, metformin decreases the amount of intracellular ROS by increasing the expression of the antioxidant protein Thioredoxin reductase (TrxR) via the AMPK-FOXO3 pathway.<sup>35</sup> Aging increases the number of mitochondrial ROS and decreases the mRNA levels of glutathione peroxidase 1 (gpx1) and sirtuin 3 (sirt3), whereas metformin has been shown to reverse these changes.<sup>36</sup>

The reduction in the number of ROS due to metformin is a multistage energy process and insulin receptor sensitization may explain how metformin can minimize ROS production while slowing the process of aging-related diseases.<sup>37</sup> Metformin decreases ROS production via reverse and through electron flux rapamycin (mTOR), which degrades superoxide and can cause DNA damage and mutations.<sup>2</sup> Mitochondrial electron transport chain (ETC) inhibition also induces AMPK-independent effects by lowering ROS, advanced glycation end products (AGEs) and reducing macromolecular damage.<sup>38</sup>

### Inhibits inflammation

Cellular and animal studies have found that metformin reduces inflammatory markers, the NF- $\kappa$ B, ROS and mTOR pathways, thereby reducing DNA damage. In addition, metformin reduces ceramide-dependent damage to myoblasts.<sup>2</sup> Metformin can inhibit chronic inflammation by improving metabolic parameters such as hyperglycemia, insulin resistance, and atherogenic dyslipidemia and has a direct anti-inflammatory effect. The AMPK-independent and senotherapeutic anti-inflammatory effects of metformin were demonstrated through downregulation of pro-inflammatory cytokines, NF- $\kappa$ B signaling, and activation of Nrf2-GPx7 signaling and mutated ataxia-telangiectasia (ATM). These three pathways reduce the dysregulation caused by aging in cells, thereby reducing the signs of aging.<sup>38</sup>

Metformin decreases inflammatory cytokines, such as TNF $\alpha$ , IL-6, and IL-1, and the inflammatory response of macrophages and induces the production of anti-inflammatory cytokines such as IL-4 and IL-10.<sup>39</sup> In patients with and without type 2 diabetes, metformin has

been shown to decrease the inflammatory mediator IL-6 and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ).<sup>39</sup> Inflammatory markers, such as interleukins and TNF, can activate various cellular processes that cause cellular and tissue damage. IL-6 can induce fibroblast proliferation and collagen production, leading to cardiac remodeling, leading to myocyte hypertrophy, and apoptosis.<sup>2</sup>

### Antioxidants

Metformin carries out its role as an antioxidant through several mechanisms, namely directly capturing hydroxyl radicals and increasing the endogenous antioxidant system, including antioxidant enzymes such as glutathione reductase, catalase, and superoxide dismutase, or GSH content and by downregulating NADPH oxidase.<sup>40</sup> Metformin has been shown to restore paraoxonase 1 (PON 1) activity, a circulating antioxidant associated with high-density lipoprotein (HDL) and hydrolyzes lipid peroxides in lipoproteins, predominantly low-density lipoprotein LDL.<sup>41</sup>

Metformin's action as an antioxidant can be explained with regard to oxidative stress. Metformin's action in delaying aging can be explained by the Nrf2 - GPx7 pathway. Nrf2 is a major transcription factor for modulating cellular antioxidant responses. By binding to antioxidant response elements (ARE), Nrf2 stimulates the expression of various antioxidant enzymes, including GPx7.<sup>32</sup> In young cells, sufficient Nrf2 transcription induces GPx7 expression to maintain oxidative stress. In old cells, the expression of Nrf2 and GPx7 are reduced and oxidative stress accumulates. The expression level of GPx7 decreases in aging human cells, and GPx7 depletion causes premature cellular aging.<sup>32</sup> The use of low-dose metformin can increase Nrf2 core translocation to increase GPx7 expression to reduce cell aging. Low-dose metformin treatment prolongs the life of human diploid fibroblasts and mesenchymal stem cells. Metformin regulates the endoplasmic reticulum GPx7. The expression level of GPx7 decreases in aging human cells, and GPx7 depletion causes premature cellular aging.<sup>32</sup>

## Autophagy pathway

Autophagy protects the nutrient supply and proper function of cell organelles. Polyamines are the most effective autophagy activators, and the induction of this process is concerned with suppression of signals along the pathway insulin-like growth factor (IGF) and mTOR.<sup>6</sup> Metformin activates protein kinase A (PRKA) and sirtuin 1 (SIRT1). Autophagy induced by the PRKA-mTOR signaling pathway unc-51-like kinase 1 (ULK1) or SIRT1-FOXO. Metformin reduces hepatosteatosis by regulating molecular interactions between SIRT1, PRKA, and autophagy. Calorie restriction and metformin upregulate SIRT1 expression and also stimulate the induction of autophagy and flux in vivo. Metformin treatment upregulates SIRT1 expression and activates PRKA even after cessation of PRKAA1/2 and siRNA-mediated SIRT1. Metformin reduces hepatic steatosis via SIRT1-mediated effects that do not depend on PRKA on the autophagy pathway.<sup>42</sup>

In the autophagy pathway, metformin inhibits mTORC1. The mTORC1 complex is a key regulator of protein synthesis through its main upstream target, S6 kinase, which initiates protein translation and synthesis. Activation of mTORC1 required Rheb (enriched homologous races in the brain) when bound to GTP. Under starvation conditions, mTORC1 is negatively regulated by tuberous sclerosis complex 2 (TSC2) and is a direct target of AMPK. Inhibition of mTORC1 by metformin occurs in an AMPK-dependent and independent.<sup>40</sup> AMPK-dependent mechanisms involve AMPK activation, which activates TSC2, the negative regulator of mTORC1. AMPK can also directly phosphorylate Raptor, a subunit of mTORC1, thereby inhibiting mTORC1 activity. AMPK activation causes indirect inhibition of mTOR so that metformin as AMPK activator has been shown to have a gastro-suppressive effect.<sup>6</sup> Metformin interacts with type V ATPase (VATPase) organelle Na<sup>+</sup>/H<sup>+</sup> exchanger (eNHE) in endosomes/lysosomes to be research results supporting indirect inhibition of mTOR.<sup>43</sup>

Metformin increases the AMP/ATP ratio leading to direct activation of

AMPK as a result of the inhibitory effect of mitochondrial complex I and causes oxidative phosphorylation. AMPK-dependent mechanisms contribute to the upstream inhibition of mTORC1 (increased nutrient sensing and autophagy), miRNA, transcriptional regulation via DNA/histone modification, and PGC-1 $\alpha$  activation (increased mitochondrial biogenesis). Extracellularly, metformin downregulates Insulin/IGF1 signaling, which also leads to inhibition of mTORC1.<sup>38</sup> AMPK can be activated by the “canonical” pathway (an increase in the ratio of adenosine diphosphate/adenosine triphosphate (ADP / ATP) and phosphorylation by LKB1 or by the AMP mechanism not directly including the lysosomal pathway induced by a decrease in fructose 1,6-bisphosphate.<sup>44</sup>

Important molecular mechanisms and aging pathways are studied to explain the anti-aging effects of metformin. Most of the clinical trial studies relating to metformin’s anti-aging effects have been conducted in animal models and are very limited in human trials. Knowledge of the anti-aging mechanisms associated with metformin in animal test models can serve as a potential developmental anti-aging agent in humans. The biomolecular involved in the mechanism pathways for the effect of metformin on anti-aging can be used as indicators in testing the anti-aging effects. Knowledge of the mechanism can also be used as a reference in metformin, which provides an effective anti-aging effect.

## CONCLUSION

In conclusion, this literature review proves that the use of metformin not only functions to reduce blood sugar levels but also have other beneficial effects, namely as an anti-aging drug. The research about metformin as an anti-aging agent is still limited, so further clinical research is needed to understand the effects of using metformin as an anti-aging agent, especially in humans.

## DISCLOSURES

### Ethical Statement

Not applicable.

## Funding

None.

## Conflict of Interest

Authors declare there is no conflict of interest regarding this article.

## Author Contribution

All authors contributed equally.

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