ISSN (Print) 1225-9918
ISSN (Online) 2287-3406
Journal of Life Science 2020 Vol. 30. No. 1. 96~105 DOI : https://doi.org/10.5352/JLS.2020.30.1.96

- Review -

A Review of Sirtuin Inhibitors in Therapeutics, Pharmaceutics, and Plant Research

Yew Lee*

Department of Molecular Biology, Dankook University, 119, Dandae-ro, Dongnam-gu, Cheonan-si, Chungnam 31116, Korea

Received September 21, 2019 / Revised January 27, 2020 / Accepted January 28, 2020

Sirtuin inhibitors are pharmaceutically and therapeutically valuable compounds that inhibit sirtuin, a type III histone deacetylase. Synthetic sirtuin inhibitors were discovered and characterized using cell-based screens in yeast (*Saccharomyces cerevisiae*) and have been used in the study of aging, carcinogenesis, and diabetes, all of which are related to sirtuin function. For medical applications, synthetic inhibitors have been further developed for increased potency and specificity, including compounds containing nicotinamide, thioacetyl lysine, β-naphthol, and indole derivatives. Suramin, tenovin, and their analogues were developed as a result. Sirtuin inhibitors were found to affect organic development and have been used to genetically modify plants, although a sirtinol-resistant mutation in the biosynthesis of a molybdopterin cofactor for an aldehyde oxidase has been identified. Some natural flavonoids, and catechin and quercetin derivatives also act as sirtuin inhibitors have been studied to identify a more potent inhibitor for therapeutic purposes. In this review, sirtuin is introduced and the therapeutic inhibitors that have been developed are presented, particularly sirtinol which has been used for genetic modification in plants though it was not designed to be so. Sirtuin inhibitors with greater potency and selectivity are required and those developed in pharmaceutics should be used in plant research to identify more authentic sirtuins in plants.

Key words : Auxin, flavonoid, sirtuin, SIRT inhibitor, therapeutic

Introduction

SIRTs are a family of NADH-dependent deacetylases and mono-ADP-ribosyl-transferase enzymes [17, 30, 42, 79, 82, 87, 88]. It catalyzes the removal of the acyl group from N^{ε}-acyl-lysine on intracellular proteins [7]. SIRTs were first discovered in yeast and they are also called Sir2 which came from the yeast gene 'silent mating-type information regulation 2' that is essential for the formation of silent heterochromatin in budding yeast [47, 72]. Yeast Sir2 deacetylates H4 lysine16, H3 lysine56, H3 lysine3, and H3 lysine14 [30, 97]. SIRTs are ubiquitous enzymes in bacteria, plants, and animals [19, 87]. SIRTs do not simply hydrolyze acetyl-lysine residues but its deacetylation reaction couples to NAD hydrolysis [5, 30, 41, 42, 82]. In animals, SIRTs are involved in a wide range of cellular processes such as aging, transcription, apoptosis, inflammation, stress resistance, and energy efficiency [53, 66, 76]. Seven SIRTs have been found in mammals [18, 51]. Mammalian SIRTs differ in subcellular location. Among them, SIRT6 is a nuclear enzyme which plays an important role in DNA damage signaling and repair and is also involved in metabolism. SIRT6 is highly expressed in human breast, prostate and skin cancer where it gives resistance to cytotoxic agents [83]. Therefore, SIRT6 is a potential therapeutic target of neurodegenerative diseases, diabetes, and cancer [36, 37, 89]. SIRT6 levels are reduced in some types of cancers [45, 78]. However, other cancers such as hepatocellular carcinoma and multiple myeloma have upregulated SIRT6 [12]. Therefore, it is worth finding the SIRT6 inhibitor for therapeutic purpose. The bioavailability of some natural flavonoids is too low to use those clinically. Therefore, there is a need for developing derivatives with better pharmacological properties. Identifying novel types of scaffolds for designing potent SIRT6 inhibitors prompted research because there are still a limited number of SIRT6 inhibitors. Human SIRTs have attracted attention because of their function in prolonging lifespan [94]. SIRT location, activity, and effect on pathologies are summarized in Carafa *et al.* [6].

Compared to mammals, knowledge about plant SIRTs is limited. SIRTs in plants are found to be involved in tissue

***Corresponding author**
Tel : +82-41-550-3480, Fax : +82-41-559-7941
E-mail : yewleesses@gmail.com

This is an Open-Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

development [20, 27], mitochondrial energy metabolism [40, 49], starch metabolism [101], synthesis and transport of auxin or auxin action [20], protection against genome stability [29], transposon silencing [29, 104], defense against *Pseudomonas syringae* [95], fruit ripening [102], and photosynthetic activity and aging of leaves [1, 9].

All SIRTs use nicotinamide adenine dinucleotide (NAD^+) as an essential cofactor [42]. Therefore, a drug which blocks the nicotinamide binding site should have clinical significance. Developing new agents that specifically inhibit the SIRT activity has had a special interest because it can give a new way to treat cancer and neurodegeneration [28, 94, 96]. However, plant scientists have used SIRT inhibitors as a tool for understanding the cellular and physiological phenomena such as hormone action, membrane trafficking, gravitropism, and plant immunity [38]. For this purpose, new chemical genetic screens have been developed to identify targets and mode of action of plant hormones, herbicides, growth regulators [38]. Furthermore, biogenic SIRT inhibitors are under investigation for pharmaceutical application.

In this review, SIRT inhibitors, synthetic and biogenic, are introduced to show how these compounds are used and for what reason and what is found in animal and plant science.

SIRT inhibitors used in therapeutics

SIRTs are involved in gene expression, metabolic control, apoptosis, DNA stability and repair, development, inflammation, neuroprotection, and aging [94]. Therefore, modulation of SIRT activity could have beneficial effects on human diseases.

Human SIRT1 (a homolog of yeast Sir2) has been described to be up-regulated in cancer cell lines [2, 96]. Therefore, SIRT inhibitors can also be potential therapeutic agents for cancer treatment. In addition to suppressing carcinogenesis, SIRT inhibitors have been proposed to use in Parkinson disease, leishmaniosis, and human immunodeficiency virus (HIV) treatment [59, 60, 93]. Because a high number of mitochondrial proteins are acetylated and deacetylated, SIRTs (SIRT3, SIRT4, SIRT5) are found to be located in mitochondria, metabolic syndrome and cancer can be treated by SIRT inhibitors [63]. There are several SIRT inhibitors developed in therapeutics (Table 1). Nicotinamide and thioacetyllysine-containing compounds are considered as mechanism-based inhibitors [22, 31, 81](Fig. 1). Other SIRT inhibitors such as β-naphthol-containing compounds (sirtinol, salermide, carbinol, splitomicin), indole derivatives (EX-527, inauhzin), sumarin, tenovin, and its analogues presumably work by noncovalent binding to the SIRT active site [28](Fig. 1). The detailed mechanism of SIRT inhibitors screened by different strategies is reviewed in other reviews [34, 71] and the effect of SIRT inhibitors on cancer development is illustrated in Fig. 2.

Sirtinol used in plant research

In plant science, SIRT inhibitor has been used for identifying the mode of action of physiological chemicals such as plant hormones, growth regulators and herbicides.

Sirtinol is an inhibitor of yeast Sir2 and human SIRT1 and SIRT2 [94]. Sirtinol was identified as an inhibitor of Sir2 in yeast by high throughput phenotypic screening of cells using small molecules [20]. Sirtinol has been used to characterize sirtinol-insensitive mutants and to identify the corresponding genes. Sirtinol was used in plants in a hope to find plant SIRT inhibitor which is involved in an epigenetic control by histone deacetylation. However, sirtinol acted deceivingly in plants and allowed to find a gene involved in sirtinol metabolism that leads to degradation of the AUX/IAA repressor and the activation of the auxin-inducible gene. Interestingly, a histone deacetylase (HDAC) trichostatin A (TSA) which does not inhibit SIRT inhibited the elongation of the primary root and stimulated the emergence of the lateral root in *Arabidopsis*, which are responses to auxin [56]. In response to TSA treatment, the level of an auxin efflux carrier PIN1 decreased in the root tip and the decrease of PIN1 was not due to the transcriptional inhibition of the *PIN1* gene [56]. Because IAA-inducible gene expression was increased by TSA treatment, the degradation of repressor AUX/IAA might be involved like the result of Zhao et al. [103]. In Nguyen et al. [56], there was no proof of a decrease in histone deacetylase activity.

Many developmentally important molecules in plants are hard to investigate their function because of the lethality and/or severe pleiotropic phenotypes of the mutants related to a certain molecule of interest. One of the molecules is plant hormone auxin. To bypass this difficulty, auxin scientists used chemical genetics to identify potent inhibitors of auxin signaling [38]. Grozinger *et al*. [20] found that sirtinol affected root and vascular development in *Arabidopsis*. Sirtinol affected the body axis formation, which is similar to the phenotype of *MONOPTEROS/AUXIN RESPONSE FACTOR5* (*MP/ARF5*) mutant [21, 67]. Later, sirtinol was found to activate the auxin-signaling pathway [103]. *Sir1* was

Table 1 SIRT inhibitors used in therapeutics

Name	Target	Treatment	Reference
Nicotinamide	SIRT1/2/3/5/6	Leukemia Prostate cancer Colon cancer	[2] [35] [86]
Thioacetyllysine-containing compounds	SIRT1/2/3	Colon cancer MCF-7 breast cancer	[85] [52]
Splitomicin	Yeast Sir2	- MCF-7 breast cancer, Fragile-X mental Retardation, HIV	[3] [55] [4] [60]
Sirtinol	Yeast Sir2, human SIRT1/2	cancer	[39, 58, 61]
AGK2	SIRT1/3	Parkinson disease, Huntingtin disease	[50, 59]
Cambinol	SIRT1, SIRT2	Burkitt lymphoma Hepatocellular carcinoma	[25] [65]
Suramin	SIRT5, SIRT1, SIRT2	trypanosomiasis	[62]
Tenovin-1 and Tenovin-6	SIRT1	Leukemia Gastric cancer	[99] [26]
Salermide	SIRT1	cancer	[44, 73]
EX-527	SIRT2, SIRT3	- Huntingtin disease Papillomavirus amplification	 [84] [43]
MC2141	SIRT1/2	Cancer	[44, 48]
Inauhzin	SIRT1	Cancer	[73]
AK-7	SIRT2	Alzheimer's, Huntington's and Parkinson's diseases	[10, 74, 90]
SDX-437	SIRT3	-	[16]

identified by chemical genetics and encodes a protein annotated as a molybdopterin synthase sulfurylase. However, part of the gene was homologous to an ubiquitin E1 ligase and a prolyl isomerase [103]. Because IAA signaling is activated by the degradation of repressive transcription factor AUX/IAA, the later explanation was convincing. Work of Zao *et al.* [103] was followed up by Dai *et al*. who drew a surprising conclusion [13]. Sirtinol-resistant mutants *sir3*, *sir4*, and *sir5* had a mutation in the gene which encodes an enzyme for the biosynthesis pathway of the molybdopterin cofactor [11]. Molybdopterin cofactor (moco) is a necessary cofactor for aldehyde oxidase and xanthine dehydrogenase, both of which play an essential role in sirtinol activities. Sirtinol undergoes a series of metabolic transformation to form 2-hydroxy-1-naphthaldehyde (HNA) and then 2-hydroxy-1-naphthoic acid (HNC) by aldehyde oxidase. HNC has striking structural similarity to a synthetic auxin 1-naphthaleneacetic acid (NAA). Therefore, *Sir* genes are required for the transformation of sirtinol into an auxin and have no role in auxin signaling and have nothing to do with deacetylase (Fig. 3).

Even though sirtinol did not lead to finding a SIRT inhibitor or a deacetylase-related protein, mutants insensitive both to sirtinol and auxin are useful. A mutant carrying a mutation in an *AtCAND1* gene encodes a HEAT-repeat protein regulating the assembly and disassembly of the SCF complex [8]. A mutation in the anticodon of a single $tRNA^{ala}$ conferred auxin resistance, which might affect the downstream auxin effectors [64]. Recently found sirtinol-resistant mutant had a mutation in a *CLEAVAGE STIMULATION FACTOR 77* (*AtCstF77*) gene which is a component of the pre-mRNA 3'-end polyadenylation machinery [100]. The *cstf77* mutant was auxin-insensitive and had a defect in polyadenylation site selection in transcripts of auxin signaling genes in *Arabidopsis* [100]. Sirtinol affected stem cell maintenance and root development in *Arabidopsis thaliana* [80]. Auxin inhibits the primary root elongation and maintains the stem cell [33, 91].

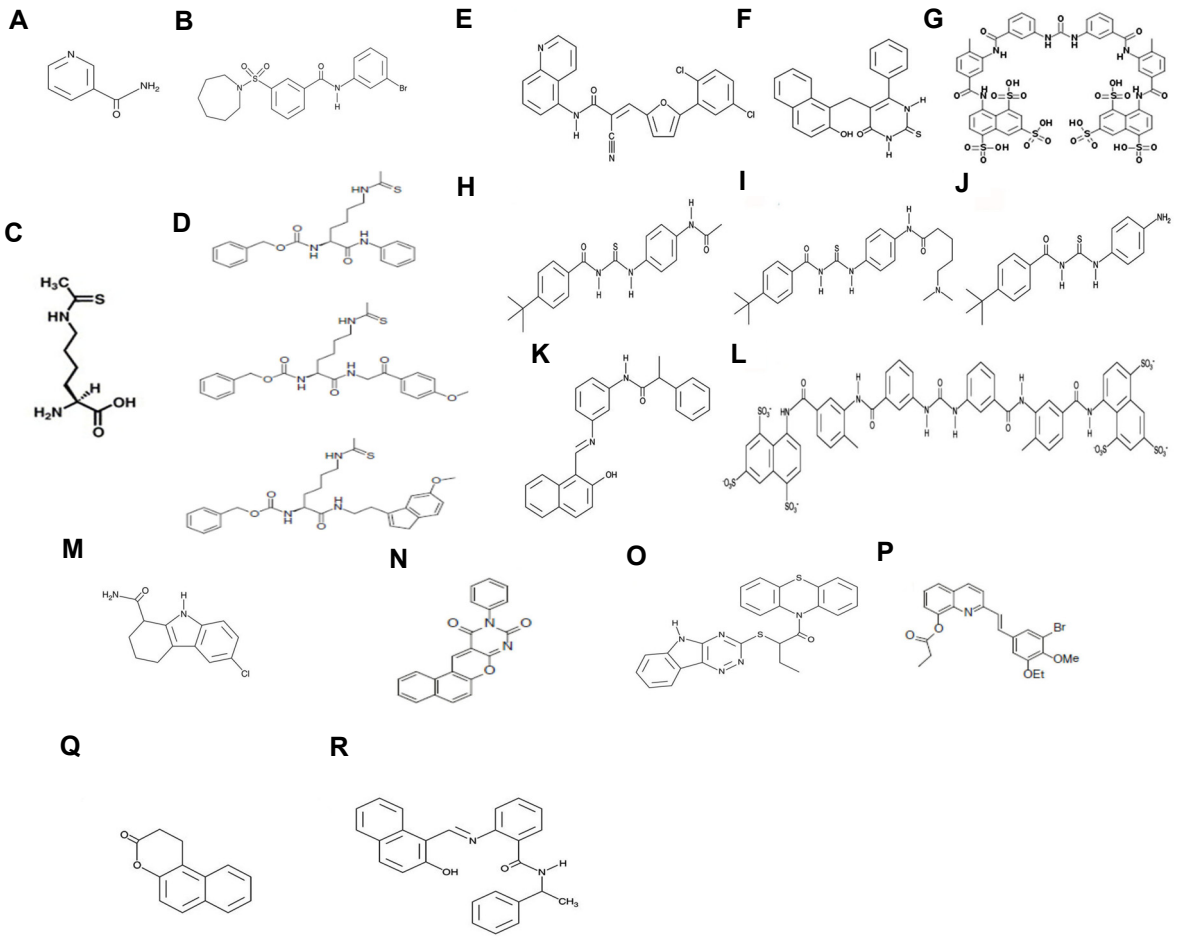

Fig. 1 SIRT inhibitors A, Nicotinamide; B, AK-7, C, Thioacetyllysine; D, Thioacetyllysine-containing compounds; E, AGK2; F, Cambinol; G, Suramin; H, Tenovin-1; I, Tenovin-6; J, Tenovin-3; K, Salermide; L, Suramin; M, EX-527; N, MC2141; O, Inauhzin; P, SDX-437; Q, Splitomicin; R, Sirtinol.

Biogenic SIRT inhibitors and their derivatives

Polyphenols are mainly natural, synthetic, semisynthetic or organic chemicals, which have multiples of phenol structural units. Polyphenols are synthesized by plants and fungi and have various pharmacological effects [24]. Polyphenols are found mainly in fruits, vegetables, cereals, and beverages, and are dietary antioxidants [46]. Polyphenols are

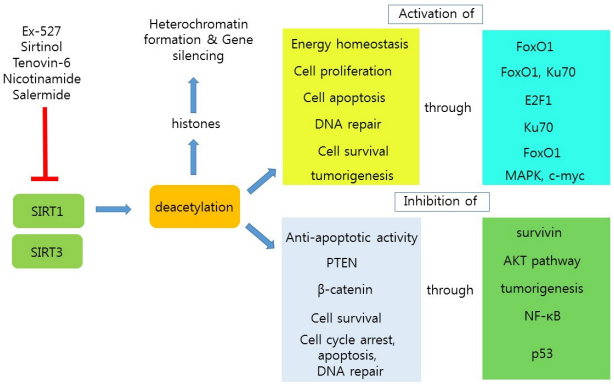

Fig. 2. Functional effect of selected SIRT inhibitors on SIRT1 and SIRT3 in cancer development.

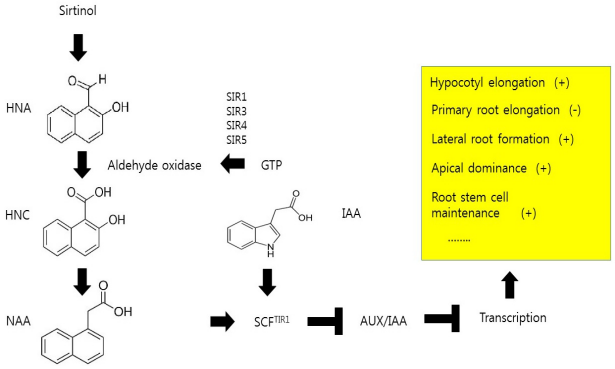

Fig. 3. Effect of sirtinol on plant development and metabolism of sirtinol to NAA by an aldehyde oxidase, requiring a molybdopterin cofactor synthesized by *Sir13*, *Sir3*, *Sir4*, and *Sir5*. (+), stimulation; (-), inhibition.

divided by two main groups, flavonoids and non-flavonoids, and more than 4,000 flavonoids have been characterized among more than 8,000 phenolic structures [46]. Because flavonoids have a plethora of biological activities, they can be used as a potential herbal medication for the treatment of several diseases and have been studied in drug development. The ability of flavonoids to modulate SIRT activity has gained interest due to the role of SIRT in aging, insulin sensitivity, lipid metabolism, inflammation, and cancer [24].

Among flavonoids, catechin and quiercetin were used to investitgate their effects as SIRT inhibitors.

Catechin is a plant secondary metabolite, which belongs to the group of flavanols, part of the chemical family flavonoids. The main source of catechin is green tea, red wine, and chocolate [46]. Catechin derivatives with galloyl moiety significantly inhibit SIRT6 at 10 μM concentration [70](Fig. 4).

Quercetin is a plant flavonol in the flavonoid group. Natural quercetin can be found in onions, leeks, and broccoli [46]. Two quercetin derivatives, diquercetin and 2-chloro-1,4-naphthoquinone-quercetin, were identified as SIRT6 inhibitors [23](Fig. 4). The IC_{50} value of diquercetin and 2-chloro-1, 4-naphtoquinone-quercetin is 130 μM and 55 μM, respectively [24]. The mode of inhibition of these inhibitors is different because diquercetin competes with nicotinamide adenine dinucleotide (NAD^+), whereas 2-chloro-1,4-naphthoquinone-quercetin competes with the acetylated substrate in the catalytic site of SIRT6 [24].

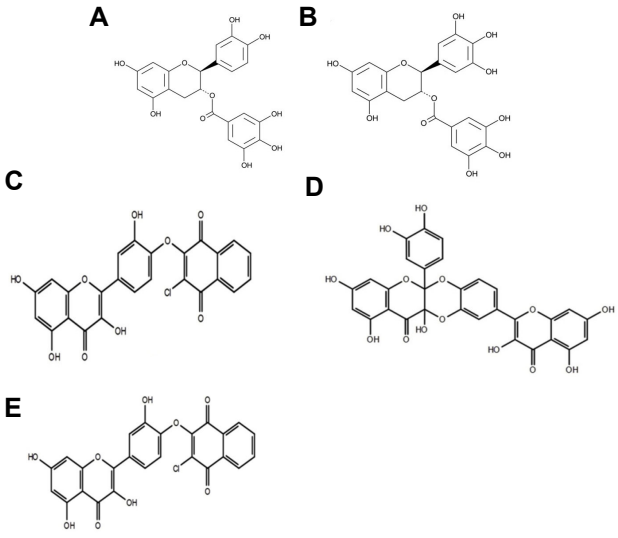

Fig. 4. Biogenic SIRT inhibitors A, (-)-Catechin gallate; B, (-)-Gallocatechin gallate; C, Quercetin; D, Diquercetin; E, Chloronathtoquinone-quercetin.

Biological roles of catechin and quiercetin in the inhibition of cancer development are illustrated in Fig. 5.

Conclusion and Perspectives

The purpose of using SIRT inhibitors is different between animals and plants. In the animal and the pharmacological field, novel SIRT inhibitors are discovered by chemical library screenings [14, 54, 59], structure-based virtual screening [68, 75, 77, 92], and the design of mechanism-based inhibitors and are used for clinical and therapeutic purpose. These inhibitors are good starting materials for making more potent and selective to each class of SIRT. More structure-activity relation should be studied.

When a SIRT inhibitor is used on plants, there should be evidence of the decrease of deacetylase activity which might influence the gene transcription of certain genes. However, regarding the auxin signal transduction pathway, more study on the relation of the action of HDAC inhibitor with protein degradation is needed. Because of the unexpected result using sirtinol, different type of SIRT inhibitors should be used to study the effect of deacetylation on plant physiology. Using different SIRT inhibitors in plants might give a way to find a deacetylase-related gene or a novel gene or a new protein.

SIRTs belong the type III histone deacetylase and all SIRTs in all organisms are divided into five classes based on a sequence of the Sir2 domain [18, 30]. Plant genomes seem to have significantly less *Sir2* homologs compared to animals, fungi, and bacteria [87]. In plants, only SIRTs belonging to class IV and class II have been identified in *Oryza sativa* (*OsSRT1* and *OsSRT2*), *Arabidopsis thaliana* (*AtSRT1* and *AtSRT2*), *Vitis vinifera* (*VvSRT2* and *VvSRT1*), and *Solanum lycopersicum* (*SlSRT1* and *SlSRT2*) [87]. Therefore, much work

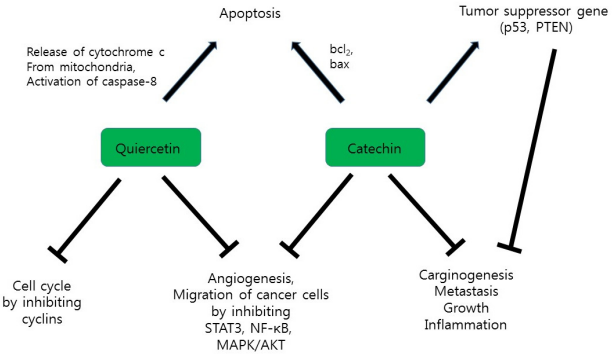

Fig. 5. Biological roles of catechin and quercetin in the inhibition of cancer development.

must be done to find the other types of SIRT HDAC, and various SIRT inhibitors should be used for this purpose. More knock-out study of other class of SIRT is also needed. Sirtinol only has been used in chemical genetics in plants. Therefore, more sirtinol inhibitors used in therapeutics might be promising to find deacetylase-related proteins or new metabolic pathways in plants. Also, the assay system for each class of SIRT must be developed in the animal and plant field.

Not all flavonoids show SIRT inhibition. Different classes of flavonoids either act as an activator or an inhibitor against SIRT. For example, catechin derivatives displayed inhibition against SIRT6, whereas cyanidin increased the SIRT6 activity [70]. In addition, kaempferol and quercetin show a dual action against SIRT6. Their activator or inhibitor action depends on substrate concentration [70]. Therefore, more study should be done to find more specific inhibitors to a certain class of SIRT. Also, deacetylation is not the only known catalytic activity of SIRTs. SIRTs show either mono-ribosyltransferase or deacylase activity [15, 32, 57, 69, 98]. A more mechanistic study is required in both animals and plants to understand the significance of various SIRT functions.

The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

References

1. Aquea, F., Timmermann, T. and Arce-Johnson, P. 2010. Analysis of histone acetyltransferase and deacetylase families of Vitis vinifera. *Plant Physiol. Biochem.* **48,** 194-199.
2. Audrito, V., Vaisitti, T., Rossi, D., Gottardi, D., D'Arena, G., Laurenti, L., Gaidano, G., Malavasi, F. and Deaglio, S. 2011. Nicotinamide blocks proliferation and induces apoptosis of chronic lymphocytic leukemia cells through activation of the p53/miR-34a/SIRT1 tumor suppressor network. *Cancer Res.* **71,** 4473-4483.
3. Bedalov, A., Gatbonton, T., Irvine, W. P., Gottschling, D. E. and Simon, J. A. 2001. Identification of a small molecule inhibitor of Sir2p. *Proc. Natl. Acad. Sci. USA.* **98,** 15113-15118.
4. Biacsi, R., Kumari, D. and Usdin, K. 2008. SIRT1 inhibition alleviates gene silencing in Fragile X mental retardation syndrome. *PLoS Genet.* **4,** e1000017.
5. Braunstein, M., Rose, A. B., Holmes, S. G., Allis, C. D. and Broach, J. R. 1993. Transcriptional silencing in yeast is associated with reduced nucleosome acetylation. *Genes Dev.* **7,** 592-604.
6. Carafa, V., Rotili, D., Forgione, M., Cuomo, F., Serretiello, E., Hailu, G. S., Jarho, E., Lahtela-Kakkonen, M., Mai, A. and Altucci, L. 2016. SIRT functions and modulation: from chemistry to the clinic. *Clin. Epigenetics* **8,** 61.
7. Chen, B., Zang, W., Wang, J., Huang, Y., He, Y., Yan, L., Liu, J. and Zheng, W. 2015. The chemical biology of SIRTs. *Chem. Soc. Rev.* **44,** 5246-5264.
8. Cheng, Y., Dai, X. and Zhao, Y. 2004. AtCAND1, a HEAT-repeat protein that participates in auxin signaling in Arabidopsis. *Plant Physiol.* **135,** 1020-1026.
9. Cucurachi, M., Busconi, M., Morreale, G., Zanetti, A., Bavaresco, L. and Fogher, C. 2012. Characterization and differential expression analysis of complete coding sequences of Vitis vinifera L. SIRT genes. *Plant Physiol. Biochem.* **54,** 123-132.
10. Cui, H., Kamal, Z., Ai, T., Xu, Y., More, S. S., Wilson, D. J. and Chen, L. 2014. Discovery of potent and selective SIRT 2 (SIRT2) inhibitors using a fragment-based approach. *J. Med. Chem.* **57,** 8340-8357.
11. Dai, X., Hayashi, K., Nozaki, H., Cheng, Y. and Zhao, Y. 2005. Genetic and chemical analyses of the action mechanisms of sirtinol in Arabidopsis. *Proc. Natl. Acad. Sci. USA.* **102,** 3129-3134.
12. Desantis, V., Lamanuzzi, A. and Vacca, A. 2018. The role of SIRT6 in tumors. *Haematologica* **103,** 1-4.
13. Dharmasiri, N., Dharmasiri, S. and Estelle, M. 2005. The F-box protein TIR1 is an auxin receptor. *Nature* **435,** 441-445.
14. Disch, J. S., Evindar, G., Chiu, C. H., Blum, C. A., Dai, H., Jin, L., Schuman, E., Lind, K. E., Belyanskaya, S. L., Deng, J., Coppo, F., Aquilani, L., Graybill, T. L., Cuozzo, J. W., Lavu, S., Mao, C., Vlasuk, G. P. and Perni, R. B. 2013. Discovery of Thieno[3,2-d]pyrimidine-6-carboxamides as Potent Inhibitors of SIRT1, SIRT2, and SIRT3. *J. Med. Chem.* **56,** 3666-3679.
15. Du, J., Zhou, Y., Su, X., Yu, J. J., Khan, S., Jiang, H., Kim, J., Woo, J., Kim, J. H., Choi, B. H., He, B., Chen, W., Zhang, S., Cerione, R. A., Auwerx, J., Hao, Q. and Lin, H. 2011. Sirt5 is a NAD-dependent protein lysine demalonylase and desuccinylase. *Science* **334,** 806-809.
16. Friden-Saxin, M., Seifert, T., Landergren, M. R., Suuronen, T., Lahtela-Kakkonen, M., Jarho, E. M. and Luthman, K. 2012. Synthesis and evaluation of substituted chroman-4-one and chromone derivatives as SIRT 2-selective inhibitors. *J. Med. Chem.* **55,** 7104-7113.
17. Frye, R. A. 1999. Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (SIRTs) metabolize NAD and may have protein ADP-ribosyltransferase activity. *Biochem. Biophys. Res. Commun.* **260,** 273-279.
18. Frye, R. A. 2000. Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins. *Biochem. Biophys. Res. Commun.* **273,** 793-798.
19. Greiss, S. and Gartner, A. 2009. SIRT/Sir2 phylogeny, evolutionary considerations and structural conservation. *Mol. Cells* **28,** 407-415.
20. Grozinger, C. M., Chao, E. D., Blackwell, H. E., Moazed,

D. and Schreiber, S. L. 2001. Identification of a class of small molecule inhibitors of the SIRT family of NAD-dependent deacetylases by phenotypic screening. *J. Biol. Chem.* **276,** 38837-38843.
21. Hardtke, C. S. and Berleth, T. 1998. The Arabidopsis gene MONOPTEROS encodes a transcription factor mediating embryo axis formation and vascular development. *EMBO J.* **17,** 1405-1411.
22. Hawse, W. F., Hoff, K. G., Fatkins, D. G., Daines, A., Zubkova, O. V., Schramm, V. L., Zheng, W. and Wolberger, C. 2008. Structural insights into intermediate steps in the Sir2 deacetylation reaction. *Structure* **16,** 1368-1377.
23. He, B., Hu, J., Zhang, X. and Lin, H. 2014. Thiomyristoyl peptides as cell-permeable Sirt6 inhibitors. *Org. Biomol. Chem.* **12,** 7498-7502.
24. Heger, V., Tyni, J., Hunyadi, A., Horakova, L., Lahtela-Kakkonen, M. and Rahnasto-Rilla, M. 2019. Quercetin based derivatives as SIRT inhibitors. *Biomed. Pharmacother.* **111,** 1326-1333.
25. Heltweg, B., Gatbonton, T., Schuler, A. D., Posakony, J., Li, H., Goehle, S., Kollipara, R., Depinho, R. A., Gu, Y., Simon, J. A. and Bedalov, A. 2006. Antitumor activity of a small-molecule inhibitor of human silent information regulator 2 enzymes. *Cancer Res.* **66,** 4368-4377.
26. Hirai, S., Endo, S., Saito, R., Hirose, M., Ueno, T., Suzuki, H., Yamato, K., Abei, M. and Hyodo, I. 2014. Antitumor effects of a SIRT inhibitor, tenovin-6, against gastric cancer cells via death receptor 5 up-regulation. *PLoS One* **9,** e102831.
27. Hollender, C. and Liu, Z. 2008. Histone deacetylase genes in Arabidopsis development. *J. Integr. Plant Biol.* **50,** 875-885.
28. Hu, J., Jing, H. and Lin, H. 2014. SIRT inhibitors as anticancer agents. *Future Med. Chem.* **6,** 945-966.
29. Huang, L., Sun, Q., Qin, F., Li, C., Zhao, Y. and Zhou, D. X. 2007. Down-regulation of a SILENT INFORMATION REGULATOR2-related histone deacetylase gene, OsSRT1, induces DNA fragmentation and cell death in rice. *Plant Physiol.* **144,** 1508-1519.
30. Imai, S., Armstrong, C. M., Kaeberlein, M. and Guarente, L. 2000. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. *Nature* **403,** 795-800.
31. Jackson, M. D., Schmidt, M. T., Oppenheimer, N. J. and Denu, J. M. 2003. Mechanism of nicotinamide inhibition and transglycosidation by Sir2 histone/protein deacetylases. *J. Biol. Chem.* **278,** 50985-50998.
32. Jiang, H., Khan, S., Wang, Y., Charron, G., He, B., Sebastian, C., Du, J., Kim, R., Ge, E., Mostoslavsky, R., Hang, H. C., Hao, Q. and Lin, H. 2013. SIRT6 regulates TNF-alpha secretion through hydrolysis of long-chain fatty acyl lysine. *Nature* **496,** 110-113.
33. Jiang, K. and Feldman, L. J. 2005. Regulation of root apical meristem development. *Annu. Rev. Cell Dev. Biol.* **21,** 485-509.
34. Jiang, Y., Liu, J., Chen, D., Yan, L. and Zheng, W. 2017. SIRT Inhibition: strategies, inhibitors, and therapeutic potential. *Trends Pharmacol. Sci.* **38,** 459-472.
35. Jung-Hynes, B., Nihal, M., Zhong, W. and Ahmad, N. 2009. Role of SIRT histone deacetylase SIRT1 in prostate cancer. A target for prostate cancer management via its inhibition? *J. Biol. Chem.* **284,** 3823-3832.
36. Kaluski, S., Portillo, M., Besnard, A., Stein, D., Einav, M., Zhong, L., Ueberham, U., Arendt, T., Mostoslavsky, R., Sahay, A. and Toiber, D. 2017. Neuroprotective functions for the histone deacetylase SIRT6. *Cell Rep.* **18,** 3052-3062.
37. Kanfi, Y., Naiman, S., Amir, G., Peshti, V., Zinman, G., Nahum, L., Bar-Joseph, Z. and Cohen, H. Y. 2012. The SIRT SIRT6 regulates lifespan in male mice. *Nature* **483,** 218-221.
38. Kaschani, F. and van der Hoorn, R. 2007. Small molecule approaches in plants. *Curr. Opin. Chem. Biol.* **11,** 88-98.
39. Kojima, K., Ohhashi, R., Fujita, Y., Hamada, N., Akao, Y., Nozawa, Y., Deguchi, T. and Ito, M. 2008. A role for SIRT1 in cell growth and chemoresistance in prostate cancer PC3 and DU145 cells. *Biochem. Biophys. Res. Commun.* **373,** 423-428.
40. Konig, A. C., Hartl, M., Pham, P. A., Laxa, M., Boersema, P. J., Orwat, A., Kalitventseva, I., Plochinger, M., Braun, H. P., Leister, D., Mann, M., Wachter, A., Fernie, A. R. and Finkemeier, I. 2014. The Arabidopsis class II SIRT is a lysine deacetylase and interacts with mitochondrial energy metabolism. *Plant Physiol.* **164,** 1401-1414.
41. Kupis, W., Palyga, J., Tomal, E. and Niewiadomska, E. 2016. The role of SIRTs in cellular homeostasis. *J. Physiol. Biochem.* **72,** 371-380.
42. Landry, J., Sutton, A., Tafrov, S. T., Heller, R. C., Stebbins, J., Pillus, L. and Sternglanz, R. 2000. The silencing protein SIR2 and its homologs are NAD-dependent protein deacetylases. *Proc. Natl. Acad. Sci. USA.* **97,** 5807-5811.
43. Langsfeld, E. S., Bodily, J. M. and Laimins, L. A. 2015. The deacetylase SIRT 1 regulates human papillomavirus replication by modulating histone acetylation and recruitment of DNA damage factors NBS1 and Rad51 to viral genomes. *PLoS Pathog.* **11,** e1005181.
44. Lara, E., Mai, A., Calvanese, V., Altucci, L., Lopez-Nieva, P., Martinez-Chantar, M. L., Varela-Rey, M., Rotili, D., Nebbioso, A., Ropero, S., Montoya, G., Oyarzabal, J., Velasco, S., Serrano, M., Witt, M., Villar-Garea, A., Imhof, A., Mato, J. M., Esteller, M. and Fraga, M. F. 2009. Salermide, a SIRT inhibitor with a strong cancer-specific proapoptotic effect. *Oncogene* **28,** 781-791.
45. Lerrer, B., Gertler, A. A. and Cohen, H. Y. 2016. The complex role of SIRT6 in carcinogenesis. *Carcinogenesis* **37,** 108-118.
46. Libro, R., Giacoppo, S., Soundara Rajan, T., Bramanti, P. and Mazzon, E. 2016. Natural phytochemicals in the treatment and prevention of dementia: an overview. *Molecules* **21,** 518.
47. Lin, S. J., Defossez, P. A. and Guarente, L. 2000. Requirement of NAD and SIR2 for life-span extension by calorie restriction in Saccharomyces cerevisiae. *Science* **289,** 2126-2128.
48. Liu, P. Y., Xu, N., Malyukova, A., Scarlett, C. J., Sun, Y. T., Zhang, X. D., Ling, D., Su, S. P., Nelson, C., Chang, D. K., Koach, J., Tee, A. E., Haber, M., Norris, M. D., Toon, C., Rooman, I., Xue, C., Cheung, B. B., Kumar, S., Marshall, G. M., Biankin, A. V. and Liu, T. 2013. The histone deacety-

lase SIRT2 stabilizes Myc oncoproteins. *Cell Death Differ.* **20,** 503-514.
49. Liu, X., Wei, W., Zhu, W., Su, L., Xiong, Z., Zhou, M., Zheng, Y. and Zhou, D. X. 2017. Histone deacetylase AtSRT1 links metabolic flux and stress response in arabidopsis. *Mol. Plant* **10,** 1510-1522.
50. Luthi-Carter, R., Taylor, D. M., Pallos, J., Lambert, E., Amore, A., Parker, A., Moffitt, H., Smith, D. L., Runne, H., Gokce, O., Kuhn, A., Xiang, Z., Maxwell, M. M., Reeves, S. A., Bates, G. P., Neri, C., Thompson, L. M., Marsh, J. L. and Kazantsev, A. G. 2010. SIRT2 inhibition achieves neuroprotection by decreasing sterol biosynthesis. *Proc. Natl. Acad. Sci. USA.* **107,** 7927-7932.
51. Marmorstein, R. 2001. Structure of histone deacetylases: insights into substrate recognition and catalysis. *Structure* **9,** 1127-1133.
52. Mellini, P., Kokkola, T., Suuronen, T., Salo, H. S., Tolvanen, L., Mai, A., Lahtela-Kakkonen, M. and Jarho, E. M. 2013. Screen of pseudopeptidic inhibitors of human SIRTs 1-3: two lead compounds with antiproliferative effects in cancer cells. *J. Med. Chem.* **56,** 6681-6695.
53. Michan, S. and Sinclair, D. 2007. SIRTs in mammals: insights into their biological function. *Biochem. J.* **404,** 1-13.
54. Napper, A. D., Hixon, J., McDonagh, T., Keavey, K., Pons, J. F., Barker, J., Yau, W. T., Amouzegh, P., Flegg, A., Hamelin, E., Thomas, R. J., Kates, M., Jones, S., Navia, M. A., Saunders, J. O., DiStefano, P. S. and Curtis, R. 2005. Discovery of indoles as potent and selective inhibitors of the deacetylase SIRT1. *J. Med. Chem.* **48,** 8045-8054.
55. Neugebauer, R. C., Uchiechowska, U., Meier, R., Hruby, H., Valkov, V., Verdin, E., Sippl, W. and Jung, M. 2008. Structure-activity studies on splitomicin derivatives as SIRT inhibitors and computational prediction of binding mode. *J. Med. Chem.* **51,** 1203-1213.
56. Nguyen, H. N., Kim, J. H., Jeong, C. Y., Hong, S. W. and Lee, H. 2013. Inhibition of histone deacetylation alters Arabidopsis root growth in response to auxin via PIN1 degradation. *Plant Cell Rep.* **32,** 1625-1636.
57. North, B. J. and Verdin, E. 2004. SIRTs: Sir2-related NAD-dependent protein deacetylases. *Genome Biol.* **5,** 224.
58. Ota, H., Tokunaga, E., Chang, K., Hikasa, M., Iijima, K., Eto, M., Kozaki, K., Akishita, M., Ouchi, Y. and Kaneki, M. 2006. Sirt1 inhibitor, Sirtinol, induces senescence-like growth arrest with attenuated Ras-MAPK signaling in human cancer cells. *Oncogene* **25,** 176-185.
59. Outeiro, T. F., Kontopoulos, E., Altmann, S. M., Kufareva, I., Strathearn, K. E., Amore, A. M., Volk, C. B., Maxwell, M. M., Rochet, J. C., McLean, P. J., Young, A. B., Abagyan, R., Feany, M. B., Hyman, B. T. and Kazantsev, A. G. 2007. SIRT 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson's disease. *Science* **317,** 516-519.
60. Pagans, S., Pedal, A., North, B. J., Kaehlcke, K., Marshall, B. L., Dorr, A., Hetzer-Egger, C., Henklein, P., Frye, R., McBurney, M. W., Hruby, H., Jung, M., Verdin, E. and Ott, M. 2005. SIRT1 regulates HIV transcription via Tat deacetylation. *PLoS Biol.* **3,** e41.
61. Peck, B., Chen, C. Y., Ho, K. K., Di Fruscia, P., Myatt, S. S., Coombes, R. C., Fuchter, M. J., Hsiao, C. D. and Lam, E. W. 2010. SIRT inhibitors induce cell death and p53 acetylation through targeting both SIRT1 and SIRT2. *Mol. Cancer Ther.* **9,** 844-855.
62. Perabo, F. G. and Muller, S. C. 2005. New agents in intravesical chemotherapy of superficial bladder cancer. *Scand. J. Urol. Nephrol.* **39,** 108-116.
63. Pereira, C. V., Lebiedzinska, M., Wieckowski, M. R. and Oliveira, P. J. 2012. Regulation and protection of mitochondrial *physiology* by SIRTs. *Mitochondrion* **12,** 66-76.
64. Perry, J., Dai, X. and Zhao, Y. 2005. A mutation in the anticodon of a single tRNAala is sufficient to confer auxin resistance in Arabidopsis. *Plant Physiol.* **139,** 1284-1290.
65. Portmann, S., Fahrner, R., Lechleiter, A., Keogh, A., Overney, S., Laemmle, A., Mikami, K., Montani, M., Tschan, M. P., Candinas, D. and Stroka, D. 2013. Antitumor effect of SIRT1 inhibition in human HCC tumor models *in vitro* and *in vivo*. *Mol. Cancer Ther.* **12,** 499-508.
66. Preyat, N. and Leo, O. 2013. SIRT deacylases: a molecular link between metabolism and immunity. *J. Leukoc. Biol.* **93,** 669-680.
67. Przemeck, G. K., Mattsson, J., Hardtke, C. S., Sung, Z. R. and Berleth, T. 1996. Studies on the role of the Arabidopsis gene MONOPTEROS in vascular development and plant cell axialization. *Planta* **200,** 229-237.
68. Pulla, V. K., Alvala, M., Sriram, D. S., Viswanadha, S., Sriram, D. and Yogeeswari, P. 2014. Structure-based drug design of small molecule SIRT1 modulators to treat cancer and metabolic disorders. *J. Mol. Graph. Model.* **52,** 46-56.
69. Rack, J. G., Morra, R., Barkauskaite, E., Kraehenbuehl, R., Ariza, A., Qu, Y., Ortmayer, M., Leidecker, O., Cameron, D. R., Matic, I., Peleg, A. Y., Leys, D., Traven, A. and Ahel, I. 2015. Identification of a class of protein ADP-Ribosylating SIRTs in microbial pathogens. *Mol. Cell.* **59,** 309-320.
70. Rahnasto-Rilla, M., Tyni, J., Huovinen, M., Jarho, E., Kulikowicz, T., Ravichandran, S., V, A. B., Ferrucci, L., Lahtela-Kakkonen, M. and Moaddel, R. 2018. Natural polyphenols as SIRT 6 modulators. *Sci. Rep.* **8,** 4163.
71. Rajabi, N., Galleano, I., Madsen, A. S. and Olsen, C. A. 2018. Targeting SIRTs: substrate specificity and inhibitor design. *Prog. Mol. Biol. Transl. Sci.* **154,** 25-69.
72. Rine, J. and Herskowitz, I. 1987. Four genes responsible for a position effect on expression from HML and HMR in Saccharomyces cerevisiae. *Genetics* **116,** 9-22.
73. Rotili, D., Tarantino, D., Nebbioso, A., Paolini, C., Huidobro, C., Lara, E., Mellini, P., Lenoci, A., Pezzi, R., Botta, G., Lahtela-Kakkonen, M., Poso, A., Steinkuhler, C., Gallinari, P., De Maria, R., Fraga, M., Esteller, M., Altucci, L. and Mai, A. 2012. Discovery of salermide-related SIRT inhibitors: binding mode studies and antiproliferative effects in cancer cells including cancer stem cells. *J. Med. Chem.* **55,** 10937-10947.
74. Rumpf, T., Schiedel, M., Karaman, B., Roessler, C., North, B. J., Lehotzky, A., Olah, J., Ladwein, K. I., Schmidtkunz, K., Gajer, M., Pannek, M., Steegborn, C., Sinclair, D. A.,

Gerhardt, S., Ovadi, J., Schutkowski, M., Sippl, W., Einsle, O. and Jung, M. 2015. Selective Sirt2 inhibition by ligand-induced rearrangement of the active site. *Nat. Commun.* **6,** 6263.

75. Sacconnay, L., Ryckewaert, L., Randazzo, G. M., Petit, C., Passos Cdos, S., Jachno, J., Michailoviene, V., Zubriene, A., Matulis, D., Carrupt, P. A., Simoes-Pires, C. A. and Nurisso, A. 2016. 5-Benzylidene-hydantoin is a new scaffold for SIRT inhibition: From virtual screening to activity assays. *Eur. J. Pharm. Sci.* **85,** 59-67.
76. Satoh, A., Brace, C. S., Ben-Josef, G., West, T., Wozniak, D. F., Holtzman, D. M., Herzog, E. D. and Imai, S. 2010. SIRT1 promotes the central adaptive response to diet restriction through activation of the dorsomedial and lateral nuclei of the hypothalamus. *J. Neurosci.* **30,** 10220-10232.
77. Schlicker, C., Boanca, G., Lakshminarasimhan, M. and Steegborn, C. 2011. Structure-based development of novel SIRT inhibitors. *Aging (Albany NY)* **3,** 852-872.
78. Sebastian, C., Zwaans, B. M., Silberman, D. M., Gymrek, M., Goren, A., Zhong, L., Ram, O., Truelove, J., Guimaraes, A. R., Toiber, D., Cosentino, C., Greenson, J. K., MacDonald, A. I., McGlynn, L., Maxwell, F., Edwards, J., Giacosa, S., Guccione, E., Weissleder, R., Bernstein, B. E., Regev, A., Shiels, P. G., Lombard, D. B. and Mostoslavsky, R. 2012. The histone deacetylase SIRT6 is a tumor suppressor that controls cancer metabolism. *Cell* **151,** 1185-1199.
79. Shore, D. 2000. The Sir2 protein family: A novel deacetylase for gene silencing and more. *Proc. Natl. Acad. Sci. USA.* **97,** 14030-14032.
80. Singh, S., Singh, A., Yadav, S., Gautam, V., Singh, A. and Sarkar, A. K. 2017. Sirtinol, a Sir2 protein inhibitor, affects stem cell maintenance and root development in Arabidopsis thaliana by modulating auxin-cytokinin signaling components. *Sci. Rep.* **7,** 42450.
81. Smith, B. C. and Denu, J. M. 2007. Mechanism-based inhibition of Sir2 deacetylases by thioacetyl-lysine peptide. *Biochemistry* **46,** 14478-14486.
82. Smith, J. S., Brachmann, C. B., Celic, I., Kenna, M. A., Muhammad, S., Starai, V. J., Avalos, J. L., Escalante-Semerena, J. C., Grubmeyer, C., Wolberger, C. and Boeke, J. D. 2000. A phylogenetically conserved NAD+-dependent protein deacetylase activity in the Sir2 protein family. *Proc. Natl. Acad. Sci. USA.* **97,** 6658-6663.
83. Sociali, G., Galeno, L., Parenti, M. D., Grozio, A., Bauer, I., Passalacqua, M., Boero, S., Donadini, A., Millo, E., Bellotti, M., Sturla, L., Damonte, P., Puddu, A., Ferroni, C., Varchi, G., Franceschi, C., Ballestrero, A., Poggi, A., Bruzzone, S., Nencioni, A. and Del Rio, A. 2015. Quinazolinedione SIRT6 inhibitors sensitize cancer cells to chemotherapeutics. *Eur. J. Med. Chem.* **102,** 530-539.
84. Sussmuth, S. D., Haider, S., Landwehrmeyer, G. B., Farmer, R., Frost, C., Tripepi, G., Andersen, C. A., Di Bacco, M., Lamanna, C., Diodato, E., Massai, L., Diamanti, D., Mori, E., Magnoni, L., Dreyhaupt, J., Schiefele, K., Craufurd, D., Saft, C., Rudzinska, M., Ryglewicz, D., Orth, M., Brzozy, S., Baran, A., Pollio, G., Andre, R., Tabrizi, S. J., Darpo, B., Westerberg, G. and Consortium, P. 2015. An exploratory double-blind, randomized clinical trial with selisistat, a SirT1 inhibitor, in patients with Huntington's disease. *Br. J. Clin. Pharmacol.* **79,** 465-476.
85. Suzuki, T., Asaba, T., Imai, E., Tsumoto, H., Nakagawa, H. and Miyata, N. 2009. Identification of a cell-active non-peptide SIRT inhibitor containing N-thioacetyl lysine. *Bioorg. Med. Chem. Lett.* **19,** 5670-5672.
86. Suzuki, T., Khan, M. N., Sawada, H., Imai, E., Itoh, Y., Yamatsuta, K., Tokuda, N., Takeuchi, J., Seko, T., Nakagawa, H. and Miyata, N. 2012. Design, synthesis, and biological activity of a novel series of human SIRT-2-selective inhibitors. *J. Med. Chem.* **55,** 5760-5773.
87. Szućko, I. 2016. SIRTs: not only animal proteins. *Acta Physiol. Plant.* **38,** 237.
88. Tanny, J. C., Dowd, G. J., Huang, J., Hilz, H. and Moazed, D. 1999. An enzymatic activity in the yeast Sir2 protein that is essential for gene silencing. *Cell* **99,** 735-745.
89. Tasselli, L., Zheng, W. and Chua, K. F. 2017. SIRT6: novel mechanisms and links to aging and disease. *Trends Endocrinol. Metab.* **28,** 168-185.
90. Taylor, D. M., Balabadra, U., Xiang, Z., Woodman, B., Meade, S., Amore, A., Maxwell, M. M., Reeves, S., Bates, G. P., Luthi-Carter, R., Lowden, P. A. and Kazantsev, A. G. 2011. A brain-permeable small molecule reduces neuronal cholesterol by inhibiting activity of SIRT 2 deacetylase. *ACS Chem. Biol.* **6,** 540-546.
91. Tromas, A. and Perrot-Rechenmann, C. 2010. Recent progress in auxin *biology*. *C. R. Biol.* **333,** 297-306.
92. Uciechowska, U., Schemies, J., Neugebauer, R. C., Huda, E. M., Schmitt, M. L., Meier, R., Verdin, E., Jung, M. and Sippl, W. 2008. Thiobarbiturates as SIRT inhibitors: virtual screening, free-energy calculations, and biological testing. *Chem. Med. Chem.* **3,** 1965-1976.
93. Vergnes, B., Vanhille, L., Ouaissi, A. and Sereno, D. 2005. Stage-specific antileishmanial activity of an inhibitor of SIR2 histone deacetylase. *Acta Trop.* **94,** 107-115.
94. Villalba, J. M. and Alcain, F. J. 2012. SIRT activators and inhibitors. *Biofactors* **38,** 349-359.
95. Wang, C., Gao, F., Wu, J., Dai, J., Wei, C. and Li, Y. 2010. Arabidopsis putative deacetylase AtSRT2 regulates basal defense by suppressing PAD4, EDS5 and SID2 expression. *Plant Cell Physiol.* **51,** 1291-1299.
96. Wang, J., Kim, T. H., Ahn, M. Y., Lee, J., Jung, J. H., Choi, W. S., Lee, B. M., Yoon, K. S., Yoon, S. and Kim, H. S. 2012. Sirtinol, a class III HDAC inhibitor, induces apoptotic and autophagic cell death in MCF-7 human breast cancer cells. *Int. J. Oncol.* **41,** 1101-1109.
97. Xu, F., Zhang, Q., Zhang, K., Xie, W. and Grunstein, M. 2007. Sir2 deacetylates histone H3 lysine 56 to regulate telomeric heterochromatin structure in yeast. *Mol. Cell.* **27,** 890-900.
98. Yamamoto, H., Schoonjans, K. and Auwerx, J. 2007. SIRT functions in health and disease. *Mol. Endocrinol.* **21,** 1745-1755.
99. Yuan, H., Wang, Z., Li, L., Zhang, H., Modi, H., Horne,

D., Bhatia, R. and Chen, W. 2012. Activation of stress response gene SIRT1 by BCR-ABL promotes leukemogenesis. *Blood* **119,** 1904-1914.
100. Zeng, W., Dai, X., Sun, J., Hou, Y., Ma, X., Cao, X., Zhao, Y. and Cheng, Y. 2019. Modulation of auxin signaling and development by polyadenylation machinery. *Plant Physiol.* **179,** 686-699.
101. Zhang, H., Lu, Y., Zhao, Y. and Zhou, D. X. 2016. OsSRT1 is involved in rice seed development through regulation of starch metabolism gene expression. *Plant Sci.* **248,** 28-36.
102. Zhao, L., Lu, J., Zhang, J., Wu, P. Y., Yang, S. and Wu, K. 2014. Identification and characterization of histone deacetylases in tomato (Solanum lycopersicum). *Front Plant Sci.* **5,** 760.
103. Zhao, Y., Dai, X., Blackwell, H. E., Schreiber, S. L. and Chory, J. 2003. SIR1, an upstream component in auxin signaling identified by chemical genetics. *Science* **301,** 1107-1110.
104. Zhong, X., Zhang, H., Zhao, Y., Sun, Q., Hu, Y., Peng, H. and Zhou, D. X. 2013. The rice NAD(+)-dependent histone deacetylase OsSRT1 targets preferentially to stress- and metabolism-related genes and transposable elements. *PLoS One* **8,** e66807.

초록 : 치료제, 조제학 및 식물을 위한 서투인 억제제의 유용성

이유*
(단국대학교 분자생물학과)

서투인 억제제는 유형 III 히스톤 데아세틸라제(HDAC)인 서투인을 억제하는 화합물이며, 약제학적 및 치료학적 가치를 갖는다. 합성 서투인 억제제는 효모 *S. cerevisiae* 에서 세포-기반 스크린을 사용하여 발견되었고 특성화되었으며 서투인의 기능과 관련된 노화, 발암 및 당뇨병을 연구하는데 사용되었다. 의학 분야에서 합성 서투인 억제제는 보다 강력한 효능과 특이성을 얻기 위해 개발되어 왔다. 니코틴아미드 및 티오아세틸리신 함유 화합물, β-나프톨 함유화합물, 인돌 유도체. 수마린, 테노빈 및 그 유사체가 개발 되었다. 서투인 억제제는 식물 발달에 영향을 미치는 것으로 밝혀졌으며 식물의 화학적 유전학에 사용되었다. 그러나, 시르티놀-내성 돌연변이 체는 알데히드 옥시다제에 대한 몰리브돕테린 보조인자의 생합성 유전자에 돌연변이가 있었다. 일부 천연 플라보노이드, 카테킨 유도체 및 퀴르세틴 유도체는 서투인 억제제로서 작용하며 치료 목적을 위한 보다 강력한 억제제를 찾기 위해 연구 되고 있다. 이 리뷰에서, 서투인을 소개하면서 치료제에서 개발된 서투인 억제제를 소개한다. 서투인 억제제인 서티놀은 식물에서 화학적 유전학에 예기치 않게 사용되었습니다. 보다 강력하고 선택적인 서투인 억제제가 치료제에서 개발되어야 하고, 약학에서 개발된 다른 서투인 억제제는 식물에서 보다 진정한 서투인을 찾기 위해 사용되어야 한다.