KASTURBA MEDICAL COLLEGE
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THE DRUG TIMES

Newsletter from Department of Pharmacology, Kasturba Medical College, Manipal
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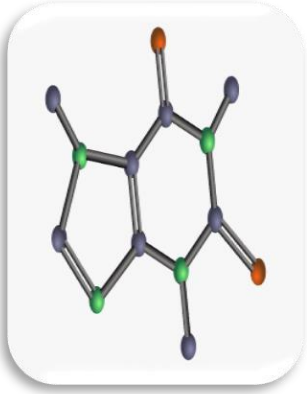
The current issue of THE DRUG TIMES provides information about artificial intelligence in pharmacovigilance, non-nutritive sugars, pharmaco fMRI, oncolytic viruses, FDA new drug approvals and anti-aging therapeutics.

Artificial Intelligence (AI) in pharmacovigilance



The word 'pharmacovigilance' was derived from the Greek literature 'pharmakon' means drug and 'vigilare' means keep watch in Latin. In artificial intelligence (AI), a computer performs tasks like human intelligence. Worldwide there is a need for monitoring the safety of drug. Spontaneous reporting is the most common method for reporting adverse drug reactions. Pharmacovigilance involves identifying and reporting of adverse drug reactions, adverse event coding, making of safety individual reports and assessing causality relationship of the suspected drug. This is time consuming. The data available globally is vast and manual analysis is difficult. So there comes the place for AI.

Machine learning-'The field of study that gives computers the ability to learn without being explicitly programmed'.

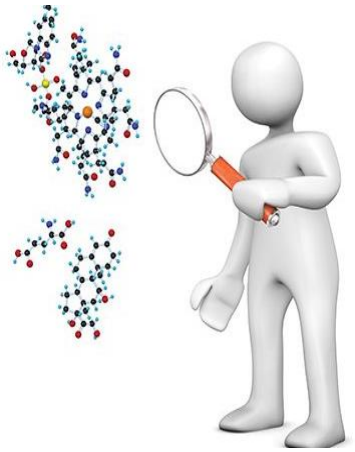
The steps can be grouped as data ingestion-related tasks, signal detection activities and lastly other applications.

Data ingestion-related tasks involves duplicate detection and causality assessment of individual case safety reports.

Later - for signal detection and analysis.

Other uses are identifying the dosage required for a patient or predicting clinical response and occurrence of ADRs.

Artificial Intelligence (AI) in pharmacovigilance
(Continued....)



Benefits of AI in Pharmacovigilance

1. Reduced cycle times makes the processing spontaneous.

2. Enhances the information quality and accuracy.

3. Handling or managing various types of incoming data formats.

4. Identification of ADRs.

5. Reduces the processing time of case reports.

6. Extraction of data from the individual case report form

With the help of AI, the overall process from the receipt of case to reporting can be automated.

Challenges of using AI in Pharmacovigilance

1. Availability of structured and curated data for training the software to identify potential drug safety issues.

2. There are privacy concerns with using AI for pharmacovigilance, as data could potentially be used for other purposes without consent from individuals involved.

References:

1. Murali K, Kaur S, Prakash A, Medhi B. Artificial intelligence in pharmacovigilance: Practical utility. Indian J Pharmacol 2019; 51:373-6

2. Andrew Bate, Jens-Ulrich Stegmann,Artificial intelligence and pharmacovigilance: What is happening, what could happen and what should happen?,Health Policy and Technology 2023; 12(2):100743.

WHO-cancer research arm has classified the low-calorie sweetener, aspartame as 'possibly carcinogenic'. This was based on limited evidence for causing liver cancer. Aspartame is 200 times sweet than sugar, and is present in more than 6000 products worldwide like diet drink, chewing gum, toothpaste and chewable vitamins.

Miryam Naddaf, Aspartame is a possible carcinogen: the science behind the decision, https://www.nature.com/articles/d41586-023-02306-0

The Sweet and Bitter aspects of Non-Nutritive Sugars

World Health Organization (WHO), in its recent guideline released in May 2023, advises against the use of non-sugar sweeteners for the purpose of risk reduction of unhealthy weight gain and prevention of diet-related non-communicable diseases.[1] Given below is an overview of non-nutritive sugars also known as high-intensity sweeteners.

> "Non-nutritive sugars" comprises of artificial and naturally derived sweeteners. These are agents which have a high intensity of sweetness but with a very low or almost no caloric value. They are highly potent in comparison with sucrose solution in their sweetening ability. With the increasing awareness among the general population about the ill effects on health due to the consumption of sugars, people are actively looking for a better replacement for sucrose. The use of these sweeteners showed a sharp rise since the 2000s with it being preferred as a healthy alternative to dietary sugars in the food and pharmaceutical industry. Non-nutritive sugars are of two types, natural and synthetic.

- Naturally derived agents include polyols (like sorbitol, erythritol, xylitol, and maltitol), stevia glycoside, thaumatin,luo han guo fruit extract, and breezin.
- Synthetic or artificial sweeteners include a wide array of agents like saccharin, cyclamate, acesulfame potassium, sucralose, aspartame, advantame, alitame, and neotame.

These agents are used widely as standalone sweeteners, a component of several food products, pharmaceutical preparations and some cosmetics. FDA has approved saccharin, aspartame, acesulfame potassium (Ace-K), sucralose, neotame, advantame, Stevia rebaudiana extract and Luo Han Guo or monk fruit extract. In India, the approved agents by the Food Safety and Standards Authority of India (FSSAI) are saccharin sodium, aspartame, acesulfame potassium, sucralose, neotame and isomaltulose.

Sweeteners	**Salient features**
Aspartame	• Most commonly used, • Shouldn't be consumed by patients with phenylketonuria (as phenylalanine is one of its breakdown products)
Neotame	• No bitter aftertaste, • Mainly used in sugar-free/low-calorie foods and beverages • Can be used in patients with phenylketonuria
Sorbitol	• In chewing gums, sweet confectionary
Advantame	• 20,000 times sweeter than sucrose, heat stable
Acesulfame potassium, Sucralose	• It remains stable even at high temperatures. Hence can be used for baking.
Saccharin	• Stable at acidic pH and high temperatures. Used extensively in processed foods

Presently, the labels on foods mention the presence of these sugars only if the amount exceeds the permissible limits set by the regulatory bodies.

Concerns with Non-nutritive sweeteners (NNS)

The first artificial sweetener, saccharin was earlier believed to cause cancer based on certain animal studies. However, studies conducted later disapproved of the same. In 2019, a group of scientists (IARC Monographs Working Group Members) categorized aspartame as "possibly carcinogenic to humans". Based on a population-based cohort study, during an eight-year follow-up, people who consumed artificial sweeteners were about 1.13 times more prone to develop cancer than the ones who never consumed them. [3]

Studies revealed a reduction in body weight with NNS in short-term use whereas there was no significant change in weight in long-term use. They have not shown to promote or aid in weight loss. Hence use of these sweeteners as a replacement for normal sugars offers no benefit to individuals who are attempting to lose weight. NNS may independently pose as a risk factor for type 2 diabetes mellitus and certain cardiovascular conditions. [4]

There is evidence to suggest that artificial sweeteners have the tendency to alter the gut microbiome and cause glucose intolerance. The consumption of these sugars is contraindicated in bowel disorders like inflammatory bowel disease, celiac disease, gluten sensitivity, etc. The diabetic population should be cautious while using it. [5] Use of NNS in pregnancy, lactation and children < 2 years of age is discouraged. [6]

Artificial sweeteners are emerging as an environmental contaminant. These compounds do not get metabolized in the body. They persist in the water bodies for a long time. It is toxic to canines (specifically Xylitol). It causes hypoglycemia by stimulating insulin release, vomiting, diarrhea, hepatic necrosis and seizures in animals. [7]

To conclude, one should bear in mind the evidence that exists with respect to the benefits and safety of high-intensity sweeteners while making them a part of the regular diet. As per the present evidence, NNS do not offer benefits in aiding weight loss or in preventing non-communicable diseases. The evidence related to harmful effects on human health should be strengthened with more studies.

References

1. Use of non-sugar sweeteners: WHO guideline. Geneva: World Health Organization; 2023.
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2. Shankar P, Ahuja S, Sriram K. Non-nutritive sweeteners: review and update. Nutrition. 2013 Nov-Dec;29(11-12):1293-9.

3. Debras C, Chazelas E, Srour B, Druesne-Pecollo N, Esseddik Y, Szabo de Edelenyi F, Agaësse C, De Sa A et al. Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study. PLoS Med. 2022 Mar 24;19(3):e1003950.

4. Garcia K, Ferreira G, Reis F, Viana S. Impact of Dietary Sugars on Gut Microbiota and Metabolic Health. Diabetology. 2022; 3(4):549-560.

5. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014;514:181–6.

6. Duffy VB, Anderson GH. Position of the American Dietetic Association: Use of nutritive and nonnutritive sweeteners. J Am Diet Assoc. 1998;98:580–7.

7. Naik AQ, Zafar T, Shrivastava VK. Environmental Impact of the Presence, Distribution, and Use of Artificial Sweeteners as Emerging Sources of Pollution. J Environ Public Health. 2021 Apr 14;2021:6624569.

Pharmaco-fMRI

Functional magnetic resonance imaging (fMRI) detects cognitive task induced functional brain maps of activation or deactivation patterns for language, motor or memory and explores disease-related effects on both localized and network-level fMRI brain maps. It may also be employed to understand drug effects on specific cognitive networks in patients on neurocognitive pharmacological therapy.

Pharmaco-fMRI studies offer surrogates biomarkers to foresee the response, drug efficacy and cognitive adverse effects of antiepileptics. Functional MRI explores the neurophysiological and anatomic mechanisms of specific behavior and stimuli on various disease conditions. It measures the neuronal activity indirectly through a signal namely Blood-Oxygen-Level-Dependent (BOLD) contrast. This signal depends on the changes in oxygenated and deoxygenated hemoglobin ratio due to metabolism produced by neuronal activity. The task-based fMRI is performed when subjects execute specifically planned cognitive tasks, test for expressive language, episodic and working memory, executive functions and sensory-motor processing.

Also, the resting-state fMRI can be used to detect spontaneous fluctuations of BOLD contrast during “rest,” or task free state. This procedure identifies functional connectivity among cortical and subcortical areas in the brain. These regions are also detected in cognitive fMRI linked with task-implicated systems. Pre-surgically, in patients with pharmaco-resistant epilepsy, fMRI along with white matter tractography is used to identify crucial brain areas connected with memory, sensori-motor functions and speech. This can help reduce risk of morbidities inflicted by surgical procedures in epilepsy. The simultaneous electroencephalography (EEG) and fMRI method can be used to localize the epileptogenic focus and aid the implantation of intracranial EEG electrodes.

Pharmaco-fMRI can assess large-scale cortical and subcortical systems, showing functional brain maps across different cognitive tasks, irrespective of the different pharmacodynamic properties. It provides mechanism-related activation and deactivation maps which can serve as targets for testing drug effects. Recent studies have made it possible to map various mechanisms underlying the cognitive adverse effects of antiepileptics. These drugs upgrade either task-related activation or task-relevant deactivation in brain maps including cortical and subcortical areas in specific epilepsy syndrome as well as brain networks involved in neurocognitive function.

***Reference**: Xiao, F., Koepp, M. J., & Zhou, D. (2019). Pharmaco-fMRI: A Tool to Predict the Response to Antiepileptic Drugs in Epilepsy. Frontiers in neurology, 10, 1203.*

FDA new drug approvals

(15th April- 15th August 2023)

	Drug	Indication	Class of drug/ Mechanism of action
1	Tofersen	Adults with amyotrophic lateral sclerosis having SOD1 gene mutation	Antisense oligonucleotide
2	Pegunigalsidase Alfa-Iwxj	Fabry disease	Hydrolytic lysosomal neutral glycosphingolipid-specific enzyme
3	Fezolinetant	Moderate to severe hot flashes due to menopause	Neurokinin 3 (NK3) receptor antagonist
4	Perfluorhexyloctane	Dry eye disease	Semifluorinated alkane
5	Epcoritamab-Bysp Glofitamab-Gxbm	Relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma	A bispecific CD20-directed CD3 T-cell engager
6	Sulbactam+ Durlobactam	Hospital-acquired and ventilator-associated bacterial pneumonia caused by Acinetobacter baumannii-calcoaceticus complex	A beta-lactam antibacterial and beta-lactamase inhibitor
7	Nirmatrelvir+ Ritonavir	Mild-to-moderate COVID-19 in adults at high risk for progression to severe COVID-19	SARS-CoV-2 Main protease inhibitor + an HIV-1 protease inhibitor and CYP3A inhibitor
8	Flotufolastat F 18	To be used along with PET imaging in select patients of prostate cancer	Binds to prostate-specific membrane antigen (PSMA)
9	Sotagliflozin	Heart failure	Sodium-glucose cotransporter 2 inhibitor
10	Ritlecitinib	Severe patchy hair loss	JAK3 and tyrosine kinase inhibitor

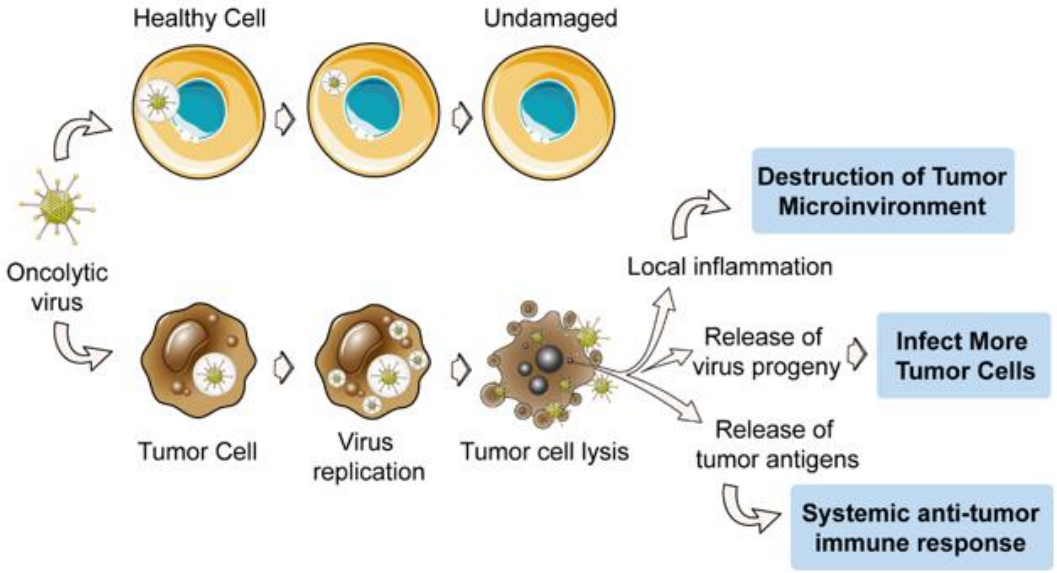
11	Rozanolixizumab-noli	Adults with Generalized myasthenia gravis (who are anti-AChr- or anti-MuSK antibody-positive)	Neonatal Fc receptor blocker
12	Somatrogon-ghla	Growth failure due to inadequate secretion of endogenous growth hormone	Growth hormone analog
13	Nirsevimab-alip	Prevention of respiratory syncytial virus infection (lower respiratory infection)	Fusion inhibitor
14	Quizartinib	Acute myeloid leukemia	Tyrosine kinase FLT3 inhibitor
15	Lotilaner	Demodex blepharitis	Inhibits GABA-chloride channels in the mite

https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2023

Viruses: An unlikely ally in the battle against cancer

In the beginning of the 20th century, doctors treating certain cancer patients noticed something strange. After a bout of viral infection, a remission, if only temporarily, was documented.[1] This gave birth to the concept of oncolytic viruses. These viruses seemed to prefer tumour cells over healthy cells. With little to no knowledge of genetic engineering, the hunt was on for naturally oncolytic viruses. Patients suffering from cervical cancer were injected with strains of adenoviruses.[2] The results were initially promising, but the immune response mounted by the body soon eliminated the virus before it could cause considerable damage to the tumour. Failure to provide any conclusive results lead to the abandonment of the concept. Better understanding of viruses along with strides in molecular biology and genetic engineering heralded a renewed interest in the latter decades of the century. [3] In 2015, T-VEC, a modified herpes virus, was FDA-approved for the treatment of unresectable metastatic stage melanoma, a landmark event.[4] Today, works on several oncolytic viruses with targets spanning almost all cancers are underway.

So how do they work? Distinguishing characteristics like activation of proto-oncogenes, inhibition of tumour suppressor genes, abnormal signaling pathways and a general sense of cellular disarray found in tumour cells make it easy for these viruses to find their way to them. It was initially thought that these viruses infected tumour cells specifically, replicated until the cells burst, spreading forth more viruses which in turn infected other tumour cells. It was later discovered that their work was being supported by our body's immune system as well. Lysed tumour cells released tumour antigen into the microenvironment; awakening the immune system that laid dormant due to the tumour until now.[5] In addition to this, viruses can be genetically tweaked to drop their pathogenic characteristics towards normal cells and improve their specificity.



Source: https://www.creative-biolabs.com/oncolytic-virus/oncolytic-virus-basis.htm

What characteristics make a good oncolytic virus? A smaller virus can penetrate barriers that larger viruses cannot, but they also become less amenable to therapeutic gene insertion. RNA viruses multiply faster than DNA viruses as they do not need to reach the nucleus to begin their work, but in turn lose out on tumour selective properties. The presence of a capsid increases their immunogenicity, resulting in their elimination even before they take effect. Apart from this, the delivery methods used must also be considered. Intra-tumoral injection provides a better safety and efficacy profile but renders it ineffective against multifocal and inaccessible tumours. Intravenous administration can seek out micro-metastatic tumours but risk exposing the viruses to the host immune system.[6]

Researchers are focusing their attention on trying to find a balance between antiviral and antitumoural immunity. Genetic modification of capsids to polyethylene glycol polymers helps to evade the circulating macrophages. Use of carrier cells to shield viruses from circulating antibodies and at the same time deliver them to target sites helps further this goal. Even so, oncolytic viruses show limited monotherapeutic results. Since the mechanism of action is wildly distinct from pre-existing anti-cancer treatment, combination therapy has been proven to show synergism, not to mention the lack of overlapping toxicity profile[7].

Oncolytic viruses are emerging as a promising novel therapeutic approach to an age-old problem, despite its drawbacks. With further breakthroughs in virotherapy and genetic engineering, and greater awareness and clinical implementation, it is easy to imagine this new modality becoming more the norm than an exception.

References

1. Dock G. "Rabies virus vaccination in a patient with cervical carcinoma." Am J Med Sci 127 (1904): 563.
2. Newman W, Southam CM. Virus treatment in advanced cancer; a pathological study of fifty-seven cases. Cancer 1954; 7:106-18.
3. Kelly E, Russell SJ. History of oncolytic viruses: genesis to genetic engineering. Mol Ther. 2007 Apr;15(4):651-9.
4. Ferrucci PF, Pala L, Conforti F, Cocorocchio E. Talimogene Laherparepvec (T-VEC): An Intralesional Cancer Immunotherapy for Advanced Melanoma. Cancers (Basel). 2021 Mar 18;13(6):1383.
5. Kaufman HL, Kohlhapp FJ, Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. Nat Rev Drug Discov. 2015 Sep;14(9):642-62.
6. Santos Apolonio J, Lima de Souza Gonçalves V, Cordeiro Santos ML, Silva Luz M, Silva Souza JV, Rocha Pinheiro SL, et al. Oncolytic virus therapy in cancer: A current review. World J Virol. 2021 Sep 25;10(5):229-55.
7. Shalhout SZ, Miller DM, Emerick KS, Kaufman HL. Therapy with oncolytic viruses: progress and challenges. Nat Rev Clin Oncol. 2023 Mar;20(3):160-177.

Potential therapeutic agents to slow down the progression of ageing

The question of ‘Do we have medicines to slow down ageing?’ has been an age-old one. Scientists and other members of the medical community have been pouring in a lot of effort and using extensive resources, to develop novel therapeutic agents to slow down the progression of ageing. In the pursuit of the same, they have discovered anti-ageing properties of existing drugs, and certain phytochemicals, many of which are produced in states of stress by plants which help tide over adverse environmental conditions.

Although the specific pathways of the ageing process are not fully understood, scientists have identified several "hallmarks" of ageing, which include: (a) genomic instability caused by DNA damage, (b)telomere attrition, (c)epigenome changes, (d)loss of healthy protein maintenance, called as proteostasis, (e)changes in metabolism causes abnormalities of regulated nutrient sensing (f)mitochondrial dysfunction, (g)accumulation of senescent cells that inflame healthy cells, (h)exhaustion of stem cells, (i)altered intercellular communication and the production of inflammatory molecules. The medications and chemicals discussed below target one or more of these "hallmarks" of ageing.

Metformin is used to treat diabetic mellitus since the late 1950s. It reduces synthesis of glucose in liver, absorption of glucose in intestine, and sensitivity to insulin increases by enhancing peripheral glucose uptake and utilization. Apart from these mechanisms, it also acts through multiple other pathways to retard the process of senescence. Metformin has been demonstrated to alter the cytokines, insulin, IGF-1 receptors and adiponectin outside of the cell, all of which are activated with ageing and, when controlled, are related with longevity. Intracellular - metformin suppresses the inflammatory pathway and activates AMPK, hence increasing mTOR inhibition, which looks to be a key target for anti-aging therapy. Through some of these processes, it also controls oxidative stress and destroys senescent cells. The above-mentioned systems have a role in inflammation, cell survival, synthesis of proteins, autophagy etc. all these have a key role in aging(1).

Alpha-ketoglutarate (AKG) is recognized to have a metabolite of anti-aging that has a capability to control many activities in life forms, hence increasing lifespan and also health span. AKG is a metabolite of tricarboxylic acid (TCA) cycle unlike other several synthetic drugs used in anti-aging. This has an influence in metabolism of cell energy, synthesis of protein, health of reproductive system and fertility, behavior of cancer cells. AKG works via few pathways including mTOR and inhibition of ATP synthase, reduction of ROS and demethylation regulation of DNA and histone.

Fisetin belongs to the flavonoid family, which is a group of naturally occurring polyphenolic chemicals. Fisetin, a strong Trolox-equivalent antioxidant, located in low levels within a range of products, including apples, persimmons, grapes, onions, and cucumbers, and in higher concentrations in strawberries. Fisetin has anti-cancer properties and appears to inhibit the PI3K/AKT/mTOR pathway. Fisetin, like other flavonoids, is a

topoisomerase inhibitor. This may also contribute to its anti-cancer activity. It boosts hSIRT1 catalytic activity, at least in vitro. Fisetin also suppresses the action of numerous pro-inflammatory cytokines in vitro like TNF, IL-6, and the transcription factor NF-B. Fisetin has direct reducing action, chemically interacting with as well as neutralizing reactive oxygen species(3).

Plants, microbes, and marine life all contain spermidine alkaloids, which typically form amide structures with cinnamic acid or fatty acid derivatives. Their unique structures exhibited a wide range of biological effects, including neuroprotective, anti-aging, anti-cancer, antioxidant, anti-inflammatory, and antibacterial capabilities(4). Aside from its pro-autophagic impact, spermidine was found to reduce various ageing-related laboratory parameters, such as ROS overproduction and necrotic cell death. Autophagy is the primary lysosomal degradation route for recycling damaged and potentially hazardous cellular material (such as faulty mitochondria). Notably, autophagy prevents cell death and increases lifespan in several ageing models. As a result, inhibiting cell death through autophagy may aid in the long-term survival of spermidine-treated cells and organisms(5).

Resveratrol, a phytoalexin, displays a response to impact, fungal infection, and ultraviolet radiation. It significantly improves the health and longevity of both yeast as well as *C. elegans* by upregulating sirtuins. It improves survival as well as proliferation of the umbilical cord stem cells of mesenchyma, in a dose dependent manner, by increasing expression of SIRT1 while the expression of p53 and p16 is suppressed. Although it has not been proven that resveratrol increases the longevity of wild-type animals, it has been found to increase the lifetime of mammals with impaired metabolism(6).

Rapamycin, belonging to macrolides, is synthesized from *Streptomyces hygroscopicus*. Initially, it was known to be an antifungal agent but research in recent times has shown that this inhibits protein kinase of mTOR and improves the average lifespan of yeast and fruit flies. Rapamycin given orally has improved the cognitive functions among old rats, reduces degeneration that occur in Alzheimer's disease. Neuronal degeneration avoidance and cognitive performance boosting both help in preserving the blood-brain barrier stoutness.

References:

1. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a Tool to Target Aging. Cell Metab. 2016 Jun 14;23(6):1060-5.

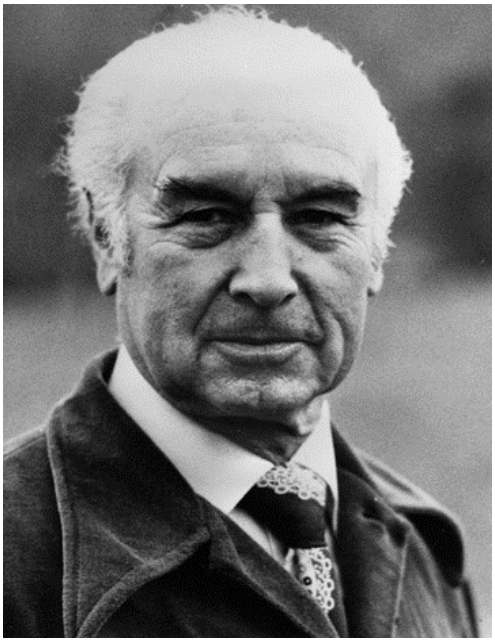
2. Naeini SH, Mavaddatiyan L, Kalkhoran ZR, Taherkhani S, Talkhabi M. Alpha-ketoglutarate as a potent regulator for lifespan and healthspan: Evidences and perspectives. Exp Gerontol. 2023 May;175:112154.

3. Yousefzadeh MJ, Zhu Y, McGowan SJ, Angelini L, Fuhrmann-Stroissnigg H, Xu M, Let al. Fisetin is a senotherapeutic that extends health and lifespan. EBioMedicine. 2018 Oct;36:18-28.

4. Shi YJ, Zhang J, Wang YW, Ding K, Yan Y, Xia CY, et al. The untapped potential of spermidine alkaloids: Sources, structures, bioactivities and syntheses. Eur J Med Chem. 2022 Oct 5;240:114600.

5. Eisenberg T, Knauer H, Schauer A, Büttner S, Ruckenstuhl C, Carmona-Gutierrez D, et al. Induction of autophagy by spermidine promotes longevity. Nat Cell Biol. 2009;11(11):1305–14.

6. Li Z, Zhang Z, Ren Y, Wang Y, Fang J, Yue H, et al. Aging and age-related diseases: from mechanisms to therapeutic strategies. Biogerontology. 2021;22(2):165–87.



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Albert Hofmann

- *A Swiss chemist*
- *Famous for the serendipitous discovery of psychedelic drug **Lysergic acid diethylamide** from Ergot*
- *Discovered **Methergine**, another ergot derivative used in post-partum haemorrhage*
- *Became an impassioned advocate for LSD as a valuable tool in psychiatry*

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