

Review Article

Dr. Yellapragada Subba Rao: an Indo-American trailblazer in the field of medicine

Sreeharshita Malla*

Indian Institute of Public Health, Hyderabad, Telangana, India

Received: 07 November 2024

Revised: 02 January 2025

Accepted: 03 January 2025

*Correspondence:

Sreeharshita Malla,

E-mail: sreeharshita.naidu.m@gmail.com

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ABSTRACT

Dr. Yellapragada Subba Rao (1895-1948) was a pioneering biochemist whose contributions have left a profound impact on modern medicine. Born into a Telugu family in India, SubbaRao's educational journey took him from Madras Medical College to prestigious institutions like Harvard Medical School and the School of Tropical Medicine, London. Despite the interruption of his medical education due to his involvement in the Indian independence movement, SubbaRao made ground-breaking advancements in biochemistry. Notably, his collaboration with Cyrus Fiske led to the development of the Fiske-Subbarow Method for phosphorus estimation and elucidated the role of phosphocreatine and ATP in muscle function. His research on vitamin B12 significantly advanced the understanding of anaemia treatment, while his work on folic acid contributed to its synthesis and therapeutic applications. SubbaRao's contributions extended to oncology and infectious diseases; his work was instrumental in developing methotrexate, an early chemotherapy drug and discovering chlortetracycline, the world's first tetracycline antibiotic. His innovative biochemical assays and research on metabolic pathways have facilitated the development of various treatments and antibiotics, fundamentally shaping the field of drug discovery and clinical practice. Despite his passing at a young age, SubbaRao's legacy endures through his significant scientific achievements and the recognition of his contributions, including tributes such as a commemorative postal stamp and the naming of species and institutions in his honour. His work remains influential in on-going research and medical applications, underscoring his role as a key figure in the advancement of biochemistry and medicine.

Keywords: Folic acid, Medical pioneer, Methotrexate, Metabolic disorders, Nutritional deficiencies, Scientific legacy, Tetracycline, Tropical medicine

INTRODUCTION

Early life and education

Dr Yellapragada Subba Rao (1895-1948) was born in an Indian Telugu family (Figure 1). After finishing Intermediate education from Presidency College, he joined Madras Medical College with interest in medicine. He attained Licentiate in Medicine and Surgery (LMS) instead of MBBS due to involvement in Indian independence movement.¹ He then joined Dr. Lakshmipathi's Ayurvedic

College at Madras as lecturer in anatomy. Fascinated by the healing powers of Ayurveda medicines, he engaged himself in research in Ayurveda. He was married to Sheshagiri, daughter of Kasturi Suryanarayana Murthy, who funded his medical education. Later, he moved to School of Tropical Medicine of London University to pursue diploma, where he worked with prominent scientists and developed his expertise in biochemistry. He joined Harvard Medical School in 1924 to work on tropical diseases.² Collaborating with Cyrus Fiske at Harvard, he developed the Fiske-Subbarow method for estimating phosphorus in body fluids and tissues.³ He also made

significant discoveries regarding the role of phosphocreatine 4 and adenosine triphosphate (ATP) in muscle activity 5 which earned him a PhD degree in June, 1929, at Harvard Commencement Program and a place in biochemistry textbooks of the 1930s.

His subsequent research work on liver extracts of pigs to find a cure for pellagra and pernicious anaemia won him a faculty appointment as Associate Professor in HMS in 1938.¹ He was given the post of director at Lederle Laboratories in 1940 to continue his research.

He passed away on August 8, 1948, due to cardiac arrest, leaving behind a significant scientific legacy that continues to benefit today's researchers in the field of drug development for various conditions.



Figure 1: Dr. Yellapragada Subbarao.²⁶

REVIEW

Contributions to the field of biochemistry

At Harvard University, Subba Rao, in collaboration with Cyrus Fiske, developed the Fiske–SubbaRow method, a groundbreaking technique for the estimation of phosphorus levels in body fluids and tissues.³ This method played a pivotal role in advancing our understanding of biochemical processes and laid the groundwork for future research in the field of biochemistry. In addition to this, Subba Rao and Fiske made significant contributions to the study of muscular activity, particularly with their discovery of the role of phosphocreatine in muscle function.⁴ Their research also led to the identification of the crucial role of adenosine triphosphate (ATP) as the primary energy source for cellular processes, an insight that revolutionized the field of cellular bioenergetics.⁵ Subba Rao's work was not confined to studies of phosphorus metabolism. He also made important strides in

the field of vitamins, particularly with his extensive research on vitamin B12. His pioneering studies on vitamin B12 were instrumental in elucidating its essential role in the formation of red blood cells, as well as its therapeutic potential. Moreover, Subba Rao's research uncovered the connection between vitamin B12 deficiency and the development of pernicious anemia, a condition that had long been poorly understood. His groundbreaking work on the biochemical mechanisms underlying vitamin B12 metabolism paved the way for the clinical application of vitamin B12 supplementation in treating pernicious anemia, thus saving countless lives and improving the overall health of patients worldwide.⁶

Later, after acquiring the position of Head of Department at Lederle Laboratories, a division of the American Cyanamid Company, Subba Rao continued to make significant contributions to medical science. During this time, he developed an efficient method for synthesizing folic acid, also known as Vitamin B9, which was a major advancement in the field.^{7,8}

This achievement built upon the earlier work of Lucy Wills, who had identified the protective effects of folic acid in preventing anemia, particularly in pregnant women. Subba Rao's research emphasized the critical role of folate in preventing a range of health issues, including neural tube defects in newborns and other complications arising from vitamin B9 deficiency. His work demonstrated the profound impact that vitamin supplementation could have on maternal and child health, leading to widespread changes in public health guidelines.

Subba Rao's personal experiences also influenced his scientific trajectory. Deeply affected by the tragic deaths of his sister and brother due to tropical sprue, a condition linked to nutritional deficiencies, he became an advocate for understanding and addressing the biochemical factors contributing to such diseases. As a result, Subba Rao was one of the first researchers to highlight the importance of folate in treating tropical sprue, further underscoring the diverse therapeutic applications of vitamins in treating malnutrition-related diseases.

In addition to his groundbreaking discoveries in vitamin research, Subba Rao also developed innovative biochemical assays for measuring vitamin levels in biological samples.^{6,7,9} These assays were not only crucial for advancing scientific research but also played a critical role in clinical diagnostics.

They enabled physicians and researchers to better understand vitamin deficiencies in patients and, as a result, facilitated the widespread adoption of vitamin supplementation as a viable and effective therapeutic strategy. Subba Rao's contributions to the development of these diagnostic tools helped shape the landscape of modern medicine, ensuring that the clinical benefits of vitamins were fully realized in the treatment of various deficiency-related diseases.

Contributions to the field of oncology and parasitology

His groundbreaking research on folic acid, in collaboration with substantial contributions from the renowned Dr. Sidney Farber, played a pivotal role in the development of methotrexate, also known as aminopterin in its earlier form. This drug, which was initially created as a treatment for cancer, has become a cornerstone of modern chemotherapy.^{10,11} Methotrexate, which works by inhibiting the action of folic acid and thereby disrupting the synthesis of DNA, continues to be widely used in the treatment of various cancers, including leukemia, lymphoma and breast cancer, among others. The significance of this discovery cannot be overstated, as it laid the foundation for subsequent advances in cancer therapy and revolutionized the way cancer is treated globally. The work of Subba Rao and Dr. Farber in this area has saved countless lives and has had a profound impact on the development of chemotherapy as we know it today. Their collaboration exemplified the potential of biomedical research to transform the medical landscape and improve patient outcomes.

In addition to his contributions to cancer treatment, Subba Rao also made significant strides in the field of parasitology. His research led to the discovery of the chemical basis for the development of diethylcarbamazine, also known as Hetrazan, an effective anthelmintic drug. Hetrazan proved to be a crucial medication in the fight against filariasis, a parasitic disease caused by thread-like nematode worms. This disease, which is prevalent in tropical and subtropical regions, can lead to debilitating conditions such as elephantiasis, causing extreme swelling in the limbs and other body parts. Subba Rao's discovery of diethylcarbamazine paved the way for the development of a treatment that not only alleviated the suffering of millions but also helped in the global effort to eliminate filariasis as a public health threat.

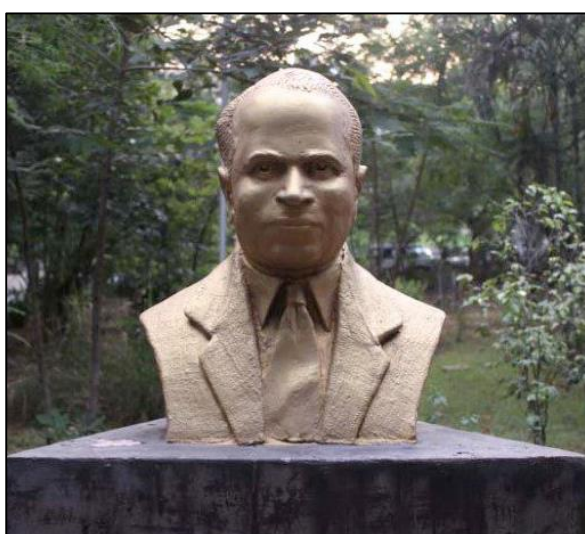


Figure 2: “Yellapragada SubbaRow’s bust in the garden of the Nizam’s Institute of Medical Sciences, Hyderabad, India”.



Figure 3: Stamp issued by Indian Postal department post his centenary (1995-1996).



Figure 4: Dr. Yellapragada Subba Rao’s portrait on the cover of Times Magazine.

The significance of Subba Rao’s work on diethylcarbamazine was further underscored when the World Health Organization (WHO) endorsed the drug for the treatment of filariasis, recognizing its effectiveness in managing and controlling the disease.¹² The widespread use of Hetrazan in endemic regions has had a lasting impact on public health, particularly in the fight against neglected tropical diseases. This endorsement by the WHO demonstrated the global importance of Subba Rao’s

research and underscored his contributions to improving healthcare in underdeveloped and developing regions. Both his contributions to cancer chemotherapy and his discoveries in the field of parasitology reflect Subba Rao's remarkable ability to apply his research to solve pressing global health issues. His work not only advanced the scientific understanding of diseases and treatments but also had tangible, life-saving effects on populations around the world. Subba Rao's contributions continue to resonate in the fields of oncology and parasitology and his legacy lives on through the therapeutic drugs that remain in widespread use to this day.

Contribution to the field of infectious diseases

Under the expert guidance of Subba Rao, Benjamin Duggar made one of the most significant breakthroughs in the field of microbiology and medicine by discovering the world's first tetracycline antibiotic, chlortetracycline, which was subsequently released under the brand name Aureomycin in 1945. This discovery marked a monumental milestone in the development of antibiotics, offering a new and powerful tool in the fight against bacterial infections. Chlortetracycline was the first antibiotic of its kind and its development was the result of a thorough investigation into the biochemical properties of soil bacteria, which led to the identification of a compound capable of inhibiting bacterial growth.¹³ Subba Rao's mentorship and scientific expertise played a crucial role in shaping Duggar's work, ensuring that the mechanisms of action of the antibiotic were well understood. This discovery opened the door to a new era in antibiotic therapy, which would prove essential in treating a broad range of bacterial diseases that were previously difficult to manage.

The release of chlortetracycline as Aureomycin had an immediate and profound impact on public health, as it became widely used in treating a variety of bacterial infections. Among its many applications, Aureomycin was instrumental in the treatment of serious and often life-threatening diseases, including plague and tuberculosis.^{14,15} The ability to combat these deadly diseases with an effective antibiotic was a turning point in medical history, significantly reducing the mortality rates associated with these infections. The development of tetracycline antibiotics, starting with chlortetracycline, paved the way for the creation of other antibiotics in the same class, which have been used extensively in the treatment of infections worldwide. Subba Rao's involvement in this critical research contributed not only to advancing scientific knowledge but also to the betterment of global public health, offering new hope to countless individuals suffering from bacterial infections.

LEGACY

His research extended far beyond the realms of vitamins and antibiotics to encompass a broader understanding of metabolism and disease. Subba Rao's extensive studies on

metabolic pathways provided crucial insights into the complex biochemical processes that govern human health. His exploration of how various metabolic imbalances—whether due to nutrient deficiencies, genetic mutations or environmental factors—could lead to a wide range of health conditions was pathbreaking. These discoveries were particularly important in understanding the underlying causes of metabolic disorders such as diabetes, obesity and various inherited diseases. By shedding light on the intricate web of biochemical reactions that sustain life, Subba Rao's work laid the foundation for future research aimed at identifying therapeutic interventions to correct or manage these imbalances. His studies helped pave the way for the development of new drugs and treatment protocols, which have been instrumental in improving the quality of life for individuals suffering from such conditions.

Throughout his illustrious career, Subba Rao was not only a pioneering researcher but also a highly influential educator and mentor. He shaped the careers of many budding biochemists and medical researchers, imparting his deep knowledge and passion for scientific discovery. His mentorship helped foster the growth of a new generation of scientists who would go on to make their own significant contributions to the field of biochemistry and medicine. Subba Rao's ability to inspire and guide his students ensured that his legacy would live on through their work.

Furthermore, his research on tetracycline antibiotics, particularly the development of chlortetracycline, had a profound and lasting impact on the field of medicine. This breakthrough revolutionized the treatment of bacterial infections, offering new hope to patients suffering from illnesses that were once fatal or difficult to treat. The success of tetracycline antibiotics paved the way for the development of other similar drugs, which have since become essential in the fight against infectious diseases. Subba Rao's work was crucial in the widespread adoption of antibiotics, which dramatically reduced mortality rates from bacterial diseases worldwide, saving millions of lives and shaping the trajectory of modern medicine.

American Cyanamid, in recognition of Dr. Yellapragada Subba Rao's immense contributions to science and medicine, honored his memory with a commemorative plaque at its research laboratory. This gesture not only celebrated his pivotal work but also ensured that his legacy would be preserved for future generations of scientists and researchers. In addition to the plaque, the company inaugurated the Subba Rao Library, a fitting tribute to a man whose career was dedicated to advancing scientific knowledge and improving global health. The establishment of the library served as a lasting reminder of his invaluable contributions to the fields of biochemistry, medicine and pharmaceutical research. His impact extended beyond his lifetime, as the library continues to serve as a resource for those seeking to build on the foundation he laid, in the world of biomedical science. The profound influence of Dr. Subba Rao was also

acknowledged by prominent media outlets, including the New York Herald Tribune, which described him as “An eminent medical mind of the century.”¹⁶ This description highlighted not only his brilliance in scientific research but also his broader impact on the medical field, where his discoveries had far-reaching consequences for the treatment of various diseases. His work was recognized not only by his peers but also by the public, who benefitted from the therapies and innovations that arose from his research. Doron Antrim, a respected journalist, poignantly captured the essence of Dr. Subba Rao's legacy in the April 1950 issue of *Argosy* magazine, following his untimely passing. In the article, Antrim wrote, “You’ve probably never heard of Dr. Yellapragada Subba Rao. Yet, because he lived, you may be alive and well today.”¹⁷ This statement served as a powerful reminder of the life-saving contributions Dr. Subba Rao made through his pioneering research, highlighting that his work had undoubtedly saved countless lives, even though his name may not be widely known outside of scientific circles.

Nobel laureate George Hitchings, in reflecting on the profound scientific impact of Dr. Yellapragada Subba Rao's work, remarked that some of the nucleotides isolated by Dr. Subba Rao had to be rediscovered years later by other researchers. Hitchings explained that this unfortunate delay in the recognition and utilization of Subba Rao's groundbreaking discoveries was partly due to the actions of Cyrus Fiske, a colleague at the time. According to Hitchings, Fiske, possibly motivated by personal jealousy or professional rivalry, did not allow Subba Rao's remarkable findings to be fully acknowledged or brought to the public's attention. As a result, some of Subba Rao's significant contributions to the field of biochemistry remained overlooked for years, preventing the immediate advancement of knowledge that could have otherwise been made.^{18,19} These discoveries, which were eventually revisited and validated by later scientists, underscore the lasting scientific value of Subba Rao's work, despite the unfortunate circumstances that hindered their initial recognition.

Hitchings' statement sheds light on the challenges Subba Rao faced during his career, particularly in the context of scientific politics, where personal rivalries sometimes overshadowed the collective progress of research. Despite these setbacks, Subba Rao's resilience and dedication to science ultimately led to the recognition of his contributions, though, tragically, much of his work was delayed in reaching its full potential. The story of how Subba Rao's crucial nucleotides were rediscovered serves as a testament to the enduring significance of his research, which was ahead of its time and should have been recognized and celebrated much earlier. Hitchings' comments not only praise Subba Rao's brilliance but also highlight the complexities and sometimes unfortunate dynamics that can influence the trajectory of scientific discovery. Methotrexate, a drug originally discovered by Dr. Yellapragada Subba Rao for its application in cancer treatment, has since proven to be an incredibly versatile

and effective medication in various medical fields. The drug, which was initially developed as part of Subba Rao's groundbreaking work on folic acid metabolism and its role in cancer therapy, has gone on to become one of the most important and widely used medications in clinical practice. Notably, Methotrexate has been approved by the United States Food and Drug Administration (FDA) and is considered one of the best treatment options available for dermatological conditions, particularly in countries like India, where it has gained popularity among healthcare providers. Its accessibility, affordability and proven effectiveness have made it a first-line treatment for managing a range of skin-related disorders, including psoriasis and Sezary syndrome, a rare form of cutaneous T-cell lymphoma.²⁰

Methotrexate's broad therapeutic benefits extend beyond its primary indications. In India, dermatologists have found it to be an essential tool for treating various off-label conditions, demonstrating its wide-reaching applications in medicine. The drug's ability to manage chronic autoimmune diseases, such as rheumatoid arthritis, as well as its role in controlling inflammatory conditions, has cemented its reputation as a reliable and cost-effective treatment. Its affordability has also made it a critical option in countries with limited access to more expensive alternatives, allowing patients to receive effective care without financial strain. As a result, Methotrexate has had a significant impact on improving the quality of life for patients worldwide, particularly in regions like India, where it continues to be a mainstay in the treatment of both dermatological and systemic conditions. Dr. Subba Rao's pioneering discovery of Methotrexate remains a testament to the lasting influence of his research and the enduring value of his contributions to medical science.

Dr. Yellapragada Subba Rao's article, titled "The Colorimetric Determination of Phosphorus," published in the prestigious *Journal of Biological Chemistry*, stands as one of the most influential and frequently cited scientific papers in the world. With over 22,000 citations to date, this article has had a profound and lasting impact on the field of biochemistry, particularly in the study of phosphorus metabolism. Subba Rao's innovative work in developing the colorimetric method for phosphorus detection not only advanced scientific knowledge but also provided researchers with a critical tool for investigating the biochemical processes that govern cellular function. The widespread adoption of this method has allowed scientists to make significant strides in various areas of biochemical research, including cellular bioenergetics and metabolic pathways, solidifying Subba Rao's place in the annals of scientific history. The article's enduring relevance underscores the depth of Subba Rao's contributions to the scientific community and it continues to serve as a foundational reference for researchers in related fields.

In honor of his extraordinary contributions to science and medicine, a bust of Dr. Subba Rao was erected at the Nizam Institute of Medical Sciences in Hyderabad, serving

as a tribute to his legacy. The installation of his bust at such a respected institution reflects the high regard in which he is held within the scientific and medical communities. It serves not only as a symbol of his invaluable contributions but also as a reminder of the enduring influence of his research on future generations of medical professionals, biochemists and students. The presence of his bust at the Nizam Institute is a poignant recognition of Subba Rao's legacy and it stands as a testament to the lasting impact of his groundbreaking work, ensuring that his contributions to science and medicine are remembered for years to come (Figure 2).

In recognition of Dr. Yellapragada Subba Rao's immense contributions to science and medicine, several honors have been bestowed upon him, solidifying his legacy in multiple fields. A genus of fungus, *Subbaromyces*, was named in his honor, acknowledging his pioneering work and lasting influence on biological research.^{21,22} Furthermore, a species of jumping spider from the genus *Tanzania*, specifically *Tanzania yellapragadai*, was named after him, illustrating the wide-reaching impact of his name within the scientific community, even in areas far removed from his direct research.²³ In addition to these biological tributes, a street in the state of Andhra Pradesh, India, was named after Dr. Subba Rao, further cementing his legacy within his home country.²⁴

These recognitions highlight the deep respect and admiration he earned, not only for his groundbreaking work but also for the global impact he had in advancing scientific and medical knowledge. His outstanding contributions to medicine were also commemorated by the Indian postal department, which launched a postal stamp bearing his image in 1995, coinciding with the centenary of his birth (Figure 3).²⁵ This prestigious honor, along with the recognition of his work in various fields, serves as a testament to the enduring influence of Dr. Subba Rao's game-changing research and the indelible mark he left on the world of science and medicine.

Dr. Yellapragada Subba Rao was widely referred to as the "Man of Miracle Drugs" due to his extraordinary contributions to the field of drug discovery, which fundamentally transformed the landscape of modern medicine. His work in identifying and developing life-saving medications, such as methotrexate, played a crucial role in advancing the treatment of cancer, autoimmune diseases and infectious diseases, among others. His groundbreaking research led to the creation of therapies that have saved countless lives and continue to be used globally. Subba Rao's unparalleled achievements in the realm of drug discovery earned him widespread recognition and he was lauded as one of the greatest scientists of all time. His ability to translate complex biochemical research into tangible medical advancements demonstrated not only his brilliance but also his profound impact on improving global public health. In addition to these prestigious accolades, Dr. Subba Rao's influence extended to the broader public, as evidenced by his portrait

being featured on the cover of Time Magazine (Figure 4). This recognition placed him among the most esteemed scientists of his era and solidified his status as a pivotal figure in the history of medicine and scientific research. The honor of appearing on such a renowned publication reflects the significance of his contributions and the widespread admiration he garnered across the world. His legacy, both in scientific circles and in the hearts of the public, continues to be celebrated as a testament to his visionary work and transformative impact on medical science.

CONCLUSION

Dr. Yellapragada Subba Rao's pioneering work in medical biochemistry, particularly his research on vitamins and antibiotics, has left an indelible mark on the field. His innovative approaches and discoveries have had a lasting impact on medicine, contributing to our understanding of nutritional deficiencies, metabolic disorders and the treatment of bacterial infections. As a medical pioneer, Subba Rao's legacy endures in the continued application and advancement of biochemistry in medicine.

His discoveries and contribution in the fields of biochemistry, oncology, pharmacology, microbiology, nutrition sciences, have paved the way for researchers of today's world of new drugs and antibiotics. His perseverance to contribute to medicine without any expectations on self-recognition and fame is commendable.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Malla S. Dr. Yellapragada Subba Rao: an Indo-American trailblazer in the field of medicine. *Int J Res Med Sci* 2025;13:927-33.