The BRICS HEALTH JOURNAL

SCIENTIFIC PEER-REVIEWED JOURNAL

VOLUME 2 • ISSUE 1 • 2025

WWW.BRICSHEALTHJOURNAL.COM ISSN 3034-4700 (Print) ISSN 3034-4719 (Online) PUBLISHED BY SECHENOV UNIVERSITY

The BRICS HEALTH JOURNAL

MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

SECHENOV UNIVERSITY LIFE SCIENCES

Volume 2 | Issue 1 | 2025 | DOI: 10.47093/3034-4700.2025.2.1

ISSN 3034-4700 (Print)
ISSN 3034-4719 (Online)

Goals and objectives: The BRICS Health Journal aims to promote medical research, public health and scientific cooperation among the BRICS countries. The publication is intended for healthcare professionals.

Founded: the journal has been published since 2024
Frequency: 4 times a year

Founders: Ministry of Health of the Russian Federation; Sechenov First Moscow State Medical University
Publisher, Editorial Office: Sechenov First Moscow State Medical University
Address: 8/2, Trubetskaya str., Moscow, 119048
Editorial office phone number: +7 (495) 609-14-00, ext.10–12
Website: https://www.bricshealthjournal.com
E-mail: bricshealthjournal@staff.sechenov.ru
DOI Prefix: 10.47093

Published: 19.05.2025

Price: flexible
Technical Editor: Daria A. Bugaeva
Editor-proofreader: Pavel P. Potapov
Page layout: Daria A. Antonova
Consulting designer: Alexander Gladkikh
Printed by: Sechenov First Moscow State Medical University
Address: 8/2, Trubetskaya str., Moscow, 119048

Format 60×90 1/8. Off set print. Print run 100 copies.

The BRICS HEALTH JOURNAL

journal homepage: https://www.bricshealthjournal.com

CONTENT

The BRICS HEALTH JOURNAL 2025; 2 (1): 3–12

journal homepage: https://www.bricshealthjournal.com
https://doi.org/10.47093/3034-4700.2025.2.1.3-12

REVIEW

Brazilian legislation on innovation policy: a brief history

Karla Regina da Silva Gram, Afrânio Lineu Kritski, Martha Maria de Oliveira, Fabricio Klerynton Marchini

ORCID numbers: Karla Regina da Silva Gram 0000-0003-3770-7504; Afrânio Lineu Kritski 0000-0002-5900-6007; Martha Maria de Oliveira 0000-0002-0064-387X; Fabricio Klerynton Marchini 0000-0001-5695-2746

Correspondence to: Karla Regina da Silva Gram, Dr., MSc, Sp., Doctoral Student, Universidade Federal do Rio de Janeiro, Tuberculosis Academic Program of the Faculty of Medicine.
Address: Rua Professor Rodolpho Paulo Rocco, 255 – 6° andar, Cidade Universitária, Rio de Janeiro, RJ, 21.941-913, Brasil;
Clinical Research Project Manager, Fundação Oswaldo Cruz, Vice-Presidência de Pesquisa e Coleções Biológicas.
Address: Avenida Brasil, 4365, Pavilhão Mourisco, sala 13, Manguinhos, Rio de Janeiro, RJ, 21.040-900, Brasil
E-mail: karla.gram@limulus.com.br

Karla Regina da Silva Gram, Dr., MSc, Sp., Doctoral Student, Universidade Federal do Rio de Janeiro, Tuberculosis Academic Program of the Faculty of Medicine. Rua Professor Rodolpho Paulo Rocco, 255 – 6° andar, Cidade Universitária, Rio de Janeiro, RJ, 21.941-913, Brasil; Clinical Research Project Manager, Fundação Oswaldo Cruz, Vice-Presidência de Pesquisa e Coleções Biológicas. Avenida Brasil, 4365, Pavilhão Mourisco, sala 13, Manguinhos, Rio de Janeiro, RJ, 21.040-900, Brasil

Afrânio Lineu Kritski, Dr., PhD, Full Professor of Phthisiology and Pulmonology, Coordinator of the Tuberculosis Academic Program at the School of Medicine and the hospital complex of the Hospital Universitário Clementino Fraga Filho/Instituto de Doenças do Tórax, Universidade Federal do Rio de Janeiro, Tuberculosis Academic Program of the Faculty of Medicine. Rua Professor Rodolpho Paulo Rocco, 255 – 6° andar, Cidade Universitária, Rio de Janeiro, RJ, 21.941-913, Brasil

Martha Maria de Oliveira, Dr., PhD, Specialist in Science, Technology, Production and Innovation in Public Health, Fundação Oswaldo Cruz, Centro de Desenvolvimento Tecnológico em Saúde. Avenida Brasil, 4036 (Campus Maré), Prédio da Expansão, 8° andar, sala 814, Manguinhos, Rio de Janeiro, RJ, 21040-361, Brasil

Fabricio Klerynton Marchini, PhD, Dr., Technological Development Manager, Instituto de Biologia Molecular do Paraná. Rua Professor Algacyr Munhoz Mader, 3775, Cidade Industrial de Curitiba, Curitiba, PR, 81350-010, Brasil; Fundação Oswaldo Cruz, Instituto Carlos Chagas. Rua Professor Algacyr Munhoz Mader, 3775, Cidade Industrial de Curitiba, Curitiba, PR, 81350-020, Brasil

Contributors: Karla Regina da Silva Gram: contributed in conceptualization, methodology, investigation, writing original draft, visualization, project administration; Afrânio Lineu Kritski: contributed in validation, review & editing, supervision; Martha Maria de Oliveira: comtributed in validation, review & editing; Fabricio Klerynton Marchini contributed in validation, review & editing. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Informed consent statement: Not required

Funding: Conselho Nacional de Desenvolvimento Científico e Tecnológico/CNPq (Public Call number 23/2018).

Competing interests: The authors declare no conflict of interest.

Ethical approval: Not required.

Data sharing: Not applicable.

ABSTRACT

Innovation is essential for socio-economic progress, particularly in today's fiercely competitive global environment. This article's primary focus is to review the evolution of Brazilian regulations on innovation policy, a subject of intense debate by the government and academic and business institutions. The goal is to review this evolution and dissect the key regulatory frameworks, policies, and initiatives shaping the current scenario. Qualitative research is carried out in three stages: searching and selecting documents, reading and categorizing sources and records, and reviewing relevant information. Since the 2000s, Brazil has promoted legislative reforms to modernize the mechanisms to encourage research and development, such as the Legal Framework for Innovation (2004), the inclusion of the term innovation in the Federal Constitution (2015), the new Legal Framework for Innovation (2016) and the National Policy for Technological Innovation in Health (2017). These changes enhance legal certainty and tax benefits for collaborations between companies and Science, Technology, and Innovation Institutions. Despite the progress, it is still crucial for Brazilian institutions to adopt more robust innovation

Acknowledgments: We offer our deepest thanks to the institutions Universidade Federal do Rio de Janeiro and Instituto de Biologia Molecular do Paraná, that provided support for the development of this manuscript.

Manuscript source: Unsolicited manuscript

Country/Territory of origin: Brazil

Received: 14.02.2025
Accepted: 15.04.2025
Date of publication: 19.05.2025

policies and more effectively align them with national development policies. Recently, the country intensified its innovation efforts by summarizing the Health Economic-Industrial Complex, integrated with the New Industrialization Policy, focused on economic, social, and sustainable development, highlighting public health. Brazil's evolution in innovation policy is a testament to the nation's steadfast commitment to technological and economic progress. While significant strides have been made, greater integration between institutions is imperative to maximize the benefits of innovation.

Key Words: innovation; innovation policy; innovation regulations; public health; normative evolution; Brazilian regulations.

Citation: Gram KR, Kritski A, de Oliveira MM, Marchini F. Brazilian legislation on innovation policy: a brief history. *The BRICS Health Journal.* 2025;2(1):3–12. https://doi.org/10.47093/3034-4700.2025.2.1.3-12

Introduction

This review aims to present the Brazilian regulatory history related to Innovation in the last twenty years and its main progress, especially in health. Understanding history is crucial for all stakeholders, as they provide a comprehensive view of the evolution of the regulatory system and the key milestones that have shaped the current scenario. Technological Innovation in healthcare has been a major catalyst, driving significant improvement that transcends borders and transforms how we care for health, preventing, diagnosing, and treating different health problems. At the heart of this innovation is the relentless search for more effective, accessible, and personalized care solutions. This includes increasing the efficiency of health systems, reducing costs, optimizing workflows, improving clinical outcomes, and seeking new or better technologies for use in medicine. The Brazilian federal government recognizes that Innovation is the key to sustainable development and that this development is only feasible with effective and coordinated public policies. Different government actions have been carried out since the early 2000s, including the sanctioning of laws and other normative documents related to Innovation. Also, it includes the recent resumption of the Health Industrial Economic Complex (in Portuguese: Complexo Econômico-Industrial da Saúde, CEIS), in 2023, and the industrial policy agenda (New Brazilian Industrialization Policy), in 2024.

Therefore, it is crucial that health professionals are well-versed in the evolution of Brazilian innovation policy regulations. This knowledge equips them to play a significant role in scientific research and healthcare, acting broadly, consciously, and collaboratively.

Objective

This paper aims to present the Brazilian regulatory history related to Innovation in the last twenty years and the main advances, especially in Health. Covering all content and knowledge related to innovation is not the aim of this review article, as the study of the conceptual and theoretical basis of innovation can be considered an established science. However, it is expected to contribute to science, knowledge and dissemination of the topics brought, both in theory and in its application, aiming to cooperate with the training of the contributors involved in the innovation

ecosystem, especially those in the health area. This paper has the potential to significantly impact the training and development of health professionals, providing them with the necessary knowledge and understanding of the Brazilian regulatory system to contribute to Innovation in the health sector effectively.

Research method

This is qualitative research, in which bibliographic research was carried out as a data source from June 2023 to June 2024. For data analysis, the 'content analysis' technique was used according to Bardin's proposition [1]. In stage 1 (pre-analysis), the search and selection of documents and articles were conducted. The data sources were documents and scientific articles available in journal databases, website searches, and the federal government, where central themes were explored, with the following entries: “innovation”, “innovation in health”, “innovation policy”, “company-institution partnerships”, “resumption of the CEIS”, and “New Brazilian Industrialization Policy”. In stage 2 (exploration of the material), the reading, selection of information sources, and systematization of ideas and categories to be reviewed were carried out. In stage 3 (information processing), the relevant information of the identified categories was reviewed and highlighted.

Results

Innovation: concepts and typology

Although it is unanimous that the idea that technological Innovation is essential for scientific development, it was only with Schumpeter, one of the most influential economists of the first half of the twentieth century, that technological Innovation began to be considered a fundamental element for economic development and a driving factor of capitalist economies. Schumpeter used the word 'innovation' to describe a series of novelties that can be introduced into the economic system and that considerably modify the relations between producers and consumers. Since then, new development theories related to innovation and schools of thought have emerged, such as the neoclassical theory with Solow (1957) and the evolutionary theory with Nelson and Winter (1974) as precursors[1].

Currently, the concept and typology of Innovation considered by most organizations around the world are those described in the Oslo Manual of the Organization for Economic Cooperation and Development (OECD). The general definition of Innovation described in the 4th edition of the Oslo Manual[2], the latest version, is: "New or improved product or process (or combination thereof) that differs significantly from the unit's previous products or processes and that has been made available (product) to potential users or put into use by the unit (process). This definition uses the generic term "unit" to describe the actor responsible for innovations. It refers to any institutional unit in any sector”.

Regarding the typology of Innovation, the third and fourth editions of the Oslo Manual differ. According to the 3rd edition of the Oslo Manual[3], Innovation can be classified into four types:

[1] Varella SRD, de Medeiros JBS, Junior MTS. O desenvolvimento da teoria da inovação Schumpeteriana. XXXII Encontro Nacional de Engenharia de Produção; Bento Gonçalves, RS, Brasil; 2012. 10 p. (In Portuguese). Accessed 07.02.2025. https://abepro.org.br/biblioteca/enegep2012_tn_sto_164_954_21021.pdf.

[2] OECD & Eurostat. Oslo Manual: Guidelines for Collecting, Reporting and Using Data on Innovation. 4th Edition. Luxembourg: OECD & Eurostat; 2018. 258 p. Accessed 07.02.2025. https://www.oecd-ilibrary.org/science-and-technology/oslo-manual-2018_9789264304604-en.

[3] OECD & Eurostat. Oslo Manual: Guidelines for Collecting and Interpreting Innovation Data. 3rd Edition. Paris, France: OECD & Eurostat; 2005. 166 p. Accessed on 07.02.2025. https://www.oecd-ilibrary.org/science-and-technology/measurement-of-scientific-and-technological-activities_9789264065581-en.

1. Product Innovation: the introduction of a new or significantly improved good or service with respect to its characteristics or intended uses. Significant improvements in technical specifications, components and materials, embedded software, ease of use, or other functional features are included.
2. Process Innovation: The implementation of a new or significantly improved production or distribution method. Significant changes in techniques, equipment, and/or software are included.
3. Marketing Innovation: It is the implementation of a new marketing method with significant changes in the design of the product or its packaging, in the positioning of the product, in its promotion or in the setting of prices.
4. Organizational Innovation: This involves implementation of a new organizational method in the company's business practices, in the organization of its workplace, or in its external relations.

The fourth edition of the Oslo Manual reduces the complexity of the "types of innovation" from four types presented in the third edition of the Oslo Manual to only two main types: "product innovations" and "business process innovations". Product innovation is a new or improved good or service that differs significantly from the company's previous goods or services and has been introduced to the market. Product innovations can use new knowledge or technologies or be based on new uses or combinations of existing ones. They are characterized by the improvement of one or all the functions or performance specifications, the improvement or addition of a new function combined with the loss of other functions, or a decline in some performance specifications. Business process innovation is a new or improved process for one or more business functions that differ significantly from the company's previous business, and that have been put into use. In this sense, business process innovations concern six different functions of a company: production of goods or services; distribution and logistics, Marketing and Sales, Information and Communication Systems, Administration and Management of products, and Business Process Development.

Within the context of the innovation system, two models of interaction between the internal research department of an organization and the external environment have recently been addressed: closed innovation and open innovation. Closed innovation is a model in which the internal research departments of organizations do not communicate with external agents (such as other companies, stakeholders, partners, consumers, or other market actors). That is to say, all innovation efforts are internal to the very borders of organizations, which are the ones that keep all intellectual property. On the other hand, in open innovation there are inputs and outputs of knowledge to accelerate the Innovation of a company or organization and expand markets[4], bringing a participatory and decentralized innovation approach [2]. Open innovation can be categorized into three types: (a) Inbound Open Innovation occurs when a company acquires and absorbs knowledge from external sources in its external innovation activities to improve its internal processes and technologies; (b) Outbound Open Innovation occurs when a company intentionally allows other companies or organizations to use, combine, or further develop its technologies, tools, or ideas for its own innovation activities and for the purpose of commercializing it. An example is when a company licenses its technol-

[4] Chesbrough HW. Open Innovation: Researching a New Paradigm. Berkeley, CA: Oxford University Press; 2005. Chapter 1, Open Innovation: A New Paradigm for Understanding Industrial Innovation; p. 1-27. Accessed 07.02.2025. https://www.academia.edu/2008513/Open_innovation_a_new_paradigm_for_understanding_industrial_innovation?auto=download.

ogy, patents, or prototypes to another company; (c) Coupled Open Innovation (or Mixed Open Innovation) is the combination of open Innovation inbound and Outbound by the same company, in which the company works in partnership with other companies/organizations to develop or commercialize innovations. Consequently, the company proactively offers to collaborate on other projects and also seeks new ideas and partnerships for its own processes[4,5].

Evolution of the Brazilian RD&I normative system

Historically, Brazil occupies a low position in the Global Innovation Index (GII) for a nation of its territorial size and economic potential. In 2011, Brazil achieved its best global position in the annually GII published by the World Intellectual Property Organization (WIPO), occupying the 47th position. However, in the following years, there was a decline, reaching the 70th position in 2015. Brazil's position improved in 2019, rising four places to 66th in the GII. With the goal of changing this scenario, Brazil has been promoting political discussions and structural reforms in its legislation since the early 2000s. These efforts aim to modernize the legal mechanisms to encourage innovation and the intellectual property system, thereby strengthening the innovation system and increasing the effectiveness of investments and activities in Research, Development, and Innovation (RD&I)[6]. Since then, the country has shown a progressive recovery. The recent GII (2023) revealed that Brazil rose from 54th (GII in 2022) to 49th position in 2023, thus occupying the leadership of the economies of Latin America and the Caribbean, a position previously held by Chile[7,8].

The Brazilian normative system in RD&I underwent significant changes at the end of 2004 when Law 10.973/2004 was sanctioned[9], known as the Federal Innovation Act and the Technological Innovation Act. Through this legal framework, public institutions were able to begin to participate effectively and legally in the innovation process, based on the regulation of technology transfer, the interaction between companies and Institutes of Science, Technology, and Innovation (ISTI), and guidance on incentives for Innovation and scientific and technological research in the productive environment. This law was initially regulated by Decree 5.563/2005, later revoked by Decree 9.283/2018, which is the current regulation in force of this law.

Subsequently, at the end of 2005, Law 11.196/2005 was sanctioned, known as the "Good Law", which creates the granting of tax incentives to legal entities that carry out research and development of technological Innovation. In other words, it is indirect financial support from the federal government, which abdicates part of the tax collection from private companies that prove to have invested in technological RD&I. These legal initiatives were driven by the considerable expansion of national programs to foster Innovation, with an increase in calls for technological innovation

[4] Chesbrough HW. Open Innovation: Researching a New Paradigm. Berkeley, CA: Oxford University Press; 2005. Chapter 1, Open Innovation: A New Paradigm for Understanding Industrial Innovation; p. 1-27. Accessed 07.02.2025. https://www.academia.edu/2008513/Open_innovation_a_new_paradigm_for_understanding_industrial_innovation?auto=download.

[5] Nerone MA, Canciglieri Junior O, Liao Y. Classification of the Open Innovation Practices: the Creativity Level. Open Access by IOS Press; 2014. Volume 1: Moving Integrated Product Development to Service Clouds in the Global Economy; p. 871–9. Accessed 07.02.2025. https://ebooks.iospress.nl/publication/37940.

[6] Lozouet L, Fonseca JC, Mazzonetto N. Guia de Melhores Práticas nas colaborações ICT-Empresas. Brasil: Brasil International Chamber of Commerce; 2020. 29 p. (In Portuguese). Accessed 07.02.2025. https://www.iccbrasil.org/wp-content/uploads/2021/09/icc_guia-de-melhores-praticas-ict-empresa_2020.pdf.

[7] Dutta S, Lanvin B, León LR, Wunsch-Vincent, S. Global Innovation Index 2023: Innovation in the face of uncertainty. Switzerland: World Intellectual Property Organization; 2023. 250 p. Accessed 07.02.2025. https://tind.wipo.int/record/48220.

[8] Dino. Brasil é 1o em inovação entre 19 países da América Latina. Valor Econômico; 20/October/2023. (In Portuguese). Accessed 07.02.2025. https://valor.globo.com/patrocinado/dino/noticia/2023/10/20/brasil-e-1o-em-inovacao-entre-19-paises-da-america-latina.ghtml.

[9] Brazil. Law 10.973, December 2, 2004. (In Portuguese). Accessed 07.02.2025. https://www.wipo.int/wipolex/en/legislation/details/19033.

projects considering ISTI-business partnerships. This innovation scenario in Brazil demanded a change in culture and adaptation of the structures and work processes of companies and ISTI to leverage successful interactions and partnerships capable of integrating knowledge in various fields of research for the generation of Innovation.

It is essential to highlight that the Federal Constitution of 1988 and Law 8.080 of 19.09.1990, did not mention "innovation" in their original texts. The introduction of the word "innovation" in the Federal Constitution of 1988 took place in 2015, through Constitutional Amendment 85 of 2015, Article 200, item V, as follows: “to increase scientific and technological development and innovation in its area of activity”. Constitutional Amendment 85 of 2015, therefore, introduced mechanisms that facilitate action in RD&I, such as allowing budget changes between capital and funding within the scope of scientific and technological projects, and assigned a more explicit role to the State in issues related to Innovation, such as encouraging the formation of partnerships between different spheres of the State, the academic sector (universities and research institutions) and the private sector.

In 2016, the new legal framework for science, technology, and Innovation was granted through Law 13.243/2016. This law, in addition to bringing its own provisions, amended nine other laws:

- Innovation Law – Law 10.973/2014
- Foreigner Statute – Law 6.815/1980 (later repealed by Law 13.445/2017)
- Bidding Law – Law 8.666/1993
- Differentiated Regime of Public Procurement Law – Law 12.462/2011
- Law of Temporary Hiring of Exceptional Public Interest – Law 8.745/1993
- Law of Support Foundations – Law 8.958/1994
- Law on the Import of Goods and Inputs for Research – Law 8.010/1990
- Law of Exemption or Reduction of Import Tax and Additional Freight for the Renewal of the Merchant Marine – Law 8.032/1990
- Law of the Career Plan of Higher Education – Law 12.772/2012

The strategic objective, at the time, was to allow more significant economic and social progress in Brazil through better use of the skills accumulated by ISTI and companies, facilitating synergistic efforts capable of making Brazil more innovative and competitive, either independently or through joint efforts with other countries[10].

In line with Law 13.243/2016, the Ministry of Science, Technology, Innovation and Communications (MSTIC) launches the "Guidance Guide for the elaboration of innovation policy in ISTI" in 201910. Built jointly by the National Forum of Innovation and Technology Transfer Managers (FORTEC) and the MSTIC, this guide aims to help ISTI managers to adapt their internal rules to the Legal Framework of Science, Technology, and Innovation. The institution of the Innovation Policy in ISTI has certainly provided greater agility and legal certainty so that the knowledge generated in academia, ISTI, and research and teaching institutions can be used by the business sector and society so that Brazil can take better advantage of this knowledge. The following year, in 2017, the National Health Innovation System received another stimulus in public policy, the institution of the "National Policy for Technological Innovation in Health" through Decree 9.245/2017. In 2020, Decree 10.534 was promulgated, which established the National Innovation Policy and provided for its governance.

[10] Martin AR et al. Guia de orientação para elaboração da política de inovação nas ICTs. Brasil: Ministério da Ciência, Tecnologia, Inovações e Comunicações/Secretaria de Empreendedorismo e Inovação; 2019. 55 p. (In Portuguese). Accessed 07.02.2025. https://repositorio.mcti.gov.br/handle/mctic/5129

Table. Key international and national documents related to R&DI in the health area.

Year	Document
1992	Oslo Manual – 1st Edition.
1996	Law 9.279 of 14.05.1996. Regulates rights and obligations related to industrial property.
1997	Oslo Manual – 2nd Edition.
1998	Decree 2.553 of 16.04.1998. Regulates articles 75 and 88 to 93 of Law 9.279 of 14.05.1996, which regulates rights and obligations related to industrial property.
2001	Law 10.196 of 14.02.2001. Amends and adds provisions to Law 9.279 of 14.05.1996, which regulates rights and obligations related to industrial property, and provides for other provisions.
2004	(Innovation Law) Law 10.973 of 02.12.2004. Provides for incentives for innovation and scientific and technological research in the productive environment and provides for other measures.
2004	Law 11.079 of 30.12.2004. Establishes general rules for bidding and contracting public-private partnerships within the scope of public administration.
2005	(Law of Good) Law 11.196 of 21.09.2005. Establishes the special tax regime for the Information Technology Services Export Platform – REPES, the Special Regime for the Acquisition of Capital Goods for Exporting Companies – RECAP and the Digital Inclusion Program; provides for tax incentives for technological innovation; amends other decrees and laws.
2005	Decree 5.563 of 11.10.2005. Regulates Law 10.973 of 02.12.2004, which provides for incentives for innovation and scientific and technological research in the productive environment, and provides for other provisions.
2005	Oslo Manual – 3rd Edition.
2006	Decree 5.798 of 07.06.2006. Regulates tax incentives for technological research and development of technological innovation activities, as provided for in articles 17 to 26 of Law 11,196 of 21.11.2005 (regulates Chapter III of the Good Law).
2006	Complementary Law 123 of 14.12.2006. Establishes the National Statute of Micro and Small Enterprises; amends provisions of Laws 8.212 and 8.213, both of 24.07.1991 of the Consolidation of Labor Laws – CLT, approved by Decree 5.452 of 01.05.1943 of Law 10.189 of 14.02.2001 of Complementary Law 63 of 11.01.1990; and repeals Laws 9.317 of 05.12.1996, and 9.841 of 05.10.1999.
2007	Decree 6.041 of 08.02.2007. Establishes the Biotechnology Development Policy, creates the National Biotechnology Committee and provides other measures.
2007	(MEC Law) Law 11.487 of 15.06.2007. Amends Law 11.196 of 21.11.2005, to include a new incentive for technological innovation and to modify the rules related to accelerated amortization for investments linked to research and development (adds article 19-A to the Good Law to include a new incentive for technological innovation in ISTI financed by companies).
2007	(FNDCT Law) Law 11.540 of 12.11.2007. Provides for the National Fund for Scientific and Technological Development – FNDCT; amends Decree 719 of 31.07.1969, and Law 9.478 of 06.08.1997; and makes other arrangements.
2011	Normative Instruction 1,187 of 29.08.2011. Regulates the tax incentives for technological research and development of technological innovation activities referred to in articles 17 to 26 of Law 11.196 of 21.11.2005 (regulates Chapter III of the Good Law).
2012	Ordinance 837 of 18.04.2012. Defines the guidelines and criteria for the establishment of Partnerships for Productive Development (PDP).
2014	Ordinance 2.531 of 12.11.2014. Redefines the guidelines and criteria for the definition of the list of strategic products for the Unified Health System (SUS) and the establishment of Partnerships for Productive Development (PDP) and regulates the respective processes of submission, instruction, decision, transfer and absorption of technology, acquisition of strategic products for the SUS within the scope of the PDP and the respective monitoring and evaluation.
2015	Constitutional Amendment 85 of 26.02.2015. Amends and adds provisions in the Federal Constitution to update the treatment of science, technology and innovation activities.
2016	Law 13.243 of 11.01.2016. Provides for incentives for scientific development, research, scientific and technological training and innovation and amends other decrees and laws (update of the Innovation Law).
2017	Law 13.529 of 20.12.2017. Provides for the participation ofthe Federal Government in a fund to support the structuring and development of concession projects and public-private partnerships; amends other decrees and laws.
2017	Decree 9.245 of December 20th, 2017. Establishes the National Policy for Technological Innovation in Health
2018	Decree 9.283 of 07.02.2018. Regulates Law 10.973 of 02.12.2004, Law 13.243 of 11.01.2016, Law 8.666 of 21.06.1993, Law 8.010 of 29.03.1990, 1990, Law 8.032, of12.04.1990; Decree 6.759 of 05.02.2009.
2018	Oslo Manual – 4th Edition.
2019	Biotechnology Roadmap 2031 for Paraná is launched at FIEP event.
2019	Publication of the Term of Reference of the National Program to Support Innovative Environments (PNI).
2019	Guidance for the elaboration of innovation policy in ISTI. Ministry of Science, Technology, Innovation and Communications (MSTIC). Secretariat of Entrepreneurship and Innovation.
2019	MSTIC Ordinance 6.762 of 17.12.2019. Establishes the National Program to Support Innovative Environments – PNI, aiming to foster the emergence and consolidation of innovation ecosystems and mechanisms for the generation of innovative enterprises in the country.

Table (Continued). Key international and national documents related to R&DI in the health area.

Year	Document
2020	Decree 10.534 of 28.10.2020. Establishes the National Innovation Policy and provides for its governance.
2021	Ordinance 4.488 of 23.02.2021. Establishes, within the scope of the MSTIC, the Brazil-Biotec Initiative and creates the Steering Committee responsible for its supervision and implementation of its objectives.
2021	Law 14.133 of 01.04.2021. Bidding and Administrative Contracts Law.
2021	CI Resolution 1 of 23.07.2021. Approves the National Innovation Strategy and the Action Plans for the Axes of Development, Technological Base, Culture of Innovation, Market for Innovative Products and Services and Educational Systems.
2021	Law 14.195 of 26.08.2021. Amends Patent Law 9279 of 1996.
2021	Law 14.200 of 02.09.2021. Amends Law 9.279 of 14.05.1996 (Industrial Property Law), to provide for the compulsory licensing of patents or patent applications in cases of declaration of national or international emergency or public interest, or recognition of a state of public calamity of national scope.
2021	SGI Resolution 001 of 23.11.2021 – Establishes the Qualifica Mais Program, within the scope of the Digital Entrepreneurship Support Plan established by Decree 5.672 of 14.09.2020.
2021	Launch of the Theoretical Appendix of the National Innovation Strategy.
2023	Ordinance 1.100 of 28.09.2023. Establishes the Innovation Policy of the National Health Surveillance Agency (Anvisa).
2023	Ordinance OM/MoH (Office of the Minister/Ministry of Health) 2.259 of 08.12.2023 – Establishes the Production and Technological Development Program for Neglected Populations and Diseases – PPDN.
2023	Ordinance OM/MoH 2.260 of 08.12.2023 – Establishes the Program for Preparation in Vaccines, Serums and Blood Products – PPVACSH.
2024	Ordinance OM/MoH 4.472 of 20.06.2024 – Amends Consolidation Ordinance OM/MoH 5 of 28.09.2017, to provide for the Partnership Program for Productive Development – PDP.
2024	Ordinance OM/MoH 4.473 of 20.06.2024 – Amends Consolidation Ordinance of Ministry of Health (MoH) of 28.09.2017 and establishes the Local Development and Innovation Program – PDIL.
2024	Ordinance OM/MoH 3.089 of 15.01.2024 – Amends OM/MoH Ordinance 2.262 of 08.12.2023, which establishes the Program for the Expansion and Modernization of Infrastructure of the Economic-Industrial Health Complex – CEIS.

In Table, a timeline is provided and outlines the history of Brazilian regulations (laws, decrees, resolutions, and others) related to RD&I, the documents that encourage Innovation in Brazil, and the primary international documents.

Among the laws to encourage Innovation in Brazil, Law 11.079/2004 stands out, and Ordinance 837 of 18.04.2012, which made the Public-Private Partnership (PPP) and the Partnerships for Productive Development (PDP) possible respectively. In Brazil, the adoption of partnerships between the public and private sectors is identified, primarily through the concession regimes of public services, especially in the areas of Health, transportation, education, and housing. In Health, partnerships focus on the works, provision of services, and management of hospital units and have shown growth in recent years; in the Unified Health System (In Portuguese: Sistema Único de Saúde, SUS), there are examples of the Suburb Hospital in Salvador/Bahia, the Barreiro Metropolitan Region Hospital in Belo Horizonte/Minas Gerais and the Modernization of the Hospital Network in São Paulo/Brazil[11]. PPP are agreements between the public and private sectors for the joint performance of a particular service or work of interest to the population. It is signed by a contract of at least five years with a value of not less than 10 million reais and in which the private company is usually responsible for the project, as well as its financing, execution, and operation. PDP are collaborations between public institutions that produce strategic health and science, technologies and innovation products and private companies, in which the Ministry of Health (MoH) guarantees partners a particular share of the public market for a

[11] CONASS. Parceria Público Privada – Guia de Apoio à Gestão Estadual do SUS. Guia de Apoio à Gestão Estadual do SUS. (In Portuguese). Accessed 07.02.2025. https://www.conass.org.br/guiainformacao/parceria-publico-privada/.

specific drug, vaccine, or health product for a certain period. On the other hand, the technology is fully transferred to the public institution. These collaborations, therefore, are intended to meet the specific demands of the SUS and to give the Brazilian State sufficient bargaining power to reduce national technological dependence[12]. Ordinance 2.531, of 12.11.2014, of the MoH determines the establishment of PDP by repealing Ordinance 837 of 18.04.2012, 2012, and consolidates the guidelines and criteria for defining the list of strategic products for acquisition by SUS. The PDP are cited as strategic instruments of the National Policy for Technological Innovation in Health in Federal Decree 9.245/2017, Subsection II. The laws that made PPP and PDP feasible were essential initiatives to promote the results of R&D efforts and foster innovation through cooperation between companies and ISTI – public and private.

Resumption of the CEIS and the new industrialization policy in Brazil

The concept of CEIS emerged in the 2000s, highlighting health as a strategic area for the country's development. Its implementation began with Minister José Gomes Temporão in 2008, with its apogee in 2011. After 2011, this experience was stagnant and resumed in 2023 as a state policy. On 26.09.2023, the "National Strategy for the Development of the Health Economic and Industrial Complex" was officially launched by the Federal Government with an investment forecast of 42.1 billion by 2026. The strategy launched has six structuring programs and aims to expand the national production of priority items for SUS and to reduce Brazil's dependence on foreign inputs, medicines, vaccines, and other health products. This seeks to give the country greater autonomy in order to reduce the vulnerability of the health sector, strengthen the local production of goods and services, reduce judicialization in Health, and stimulate job creation in the sector[13]. One of the priorities is to support the production of inputs for the prevention, diagnosis, and treatment of socially determined diseases, such as tuberculosis, Chagas disease, viral hepatitis, and HIV. Another priority is addressing diseases relevant to public health, including chronic diseases (cancer, cardiovascular, diabetes, and immunological), dengue, health emergencies, and orthopedic trauma. In 2023, the health sector accounted for 10% of the Gross Domestic Product (GDP) and accounted for a third of scientific research in the country. However, Brazil's dependence on health inputs makes SUS vulnerable to the foreign market; namely, more than 90% of the raw material used in Brazil to produce vaccine and medicine inputs is imported. In the area of medical equipment, the national production is at 50%; in medicines, it is about 60%, and in vaccines, it is higher. The goal, with the investment foreseen in the strategy launched, is to reach an average of 70% of national production in the health sector[13].

The National Strategy for the Development of the CEIS is integrated into the effort to implement the New Policy for the Development of the Brazilian Industrial Sector, presented by the federal government in January 2024, whose guidelines are aimed at the economic, social, and sustainable development of Brazil. The new policy has the following measures: creation of memorable credit lines, grants, regulatory actions, intel-

[12] Gadelha C. Dinâmica global, impasses do SUS e o CEIS como saída estruturante da crise. Resgate. 16/novembro/2021 [Atualizado 15/02/2022]. (In Portuguese). Accessed 07.02.2025. https://outraspalavras.net/resgate/2021/11/16/dinamica-global-impasses-do-sus-e-o-ceis-como-saida-estruturante-da-crise/.

[13] Ministério da Saúde, Brasil. Governo Federal lança Estratégia Nacional para o Desenvolvimento do Complexo Econômico-Industrial da Saúde com investimento de R$ 42 bilhões até 2026. Brasil: Portal do Governo Federal – Ministério da Saúde; 26/setembro/2023 [Atualizado em 27/setembro/2023]. (In Portuguese). Accessed 07.02.2025. https://www.gov.br/saude/pt-br/assuntos/noticias/2023/setembro/governo-federal-lanca-estrategia-nacional-para-o-desenvolvimento-do-complexo-economico-industrial-da-saude-com-investimento-de-r-42-bilhoes-ate-2026.

lectual property actions, and policy of public works and purchases (with incentives for local content) to stimulate the productive sector. The goals are grouped into six missions that guide efforts until 2033, in which Mission 2 stands out referring to the CEIS[14]. Along with the policy, the National Council for Industrial Development delivered the action plan for the period 2024-2026, indicating the priority strategic areas for the application of resources.

The current New Brazilian Industrialization Policy and government actions to encourage Innovation in Brazil predicts the country's rise in the GII in the coming years. These actions include revisions to the current RD&I regulations and public policies to encourage partnerships between companies and ISTI, such as: Public Consultation 53/2023 DECEIIS/SECTICS – Local Development and Innovation Program – PDIL (extended by CP 55, of 12.22.2023, Official Gazette of 01.02.2024, Section 1, page 156); Public Consultation 54/2023 DECEIIS/SECTICS/MoH – Partnership Program for Productive Development – PDP (extended by CP 56, of 12.26.2023, Official Gazette of 12.28.2023, Section 1, p. 174).

Conclusions

In the current techno-productive paradigm, innovating is a matter of survival and, at the same time, sovereignty in the market. "Not innovating" incurs a high risk of deterioration in the competitive performance of the company or institution. Since the early 2000s, Brazil has been increasing policy actions and promoting structural reforms in its legislation to modernize the legal mechanisms to encourage RD&I, including the intellectual property system. Noteworthy is the establishment of the Legal Framework for Innovation in 2004, the inclusion of the term innovation in the Federal Constitution in 2015, the new Legal Framework for Innovation in 2016, and the National Policy for Technological Innovation in Health in 2017, which offer greater legal certainty and tax incentives for the establishment of partnerships between companies and ISTIs. Despite all these efforts, it is still urgent and necessary for Brazilian institutions to adopt an innovation policy as a reflection of the consensus that the efforts to boost Innovation in Brazil depend on the participation of ISTI and their more incredible insertion in national and local development policies. Brazil has recently intensified the innovation movement with the resumption of the CEIS (2023) integrated with the New Brazilian Industrialization Policy (2024), whose guidelines focus on the economic, social, and sustainable development of Brazil, with particular attention to the area of public Health.

References

1. Bardin L. Análise de Conteúdo. 1st Edition. São Paulo, Brasil: *Edições 70*. 2015; 288 p.
2. Chesbrough HW. Open Innovation: The New Imperative for Creating and Profiting from Technology. Boston, Massachusetts: *Harvard Business School Press*. 2003; 227 p.

[14] Ministério do Desenvolvimento, Indústria, Comércio e Serviços, Brasil. Brasil ganha nova política industrial com metas e ações para o desenvolvimento até 2033. Brasil: Portal do Governo Federal – Ministério do Desenvolvimento, Indústria, Comércio e Serviços; 22/janeiro/2024 [Atualizado em 23/janeiro/2024]. (In Portuguese). Accessed on 07.02.2025. https://www.gov.br/mdic/pt-br/assuntos/noticias/2024/janeiro/brasil-ganha-nova-politica-industrial-com-metas-e-acoes-para-o-desenvolvimento-ate-2033.

The BRICS HEALTH JOURNAL 2025; 2 (1): 13-26

journal homepage: https://www.bricshealthjournal.com
https://doi.org/10.47093/3034-4700.2025.2.1.13-26

REVIEW

From global practice to national strategy: horizon scanning tools for healthcare transformation in Russia

Nuriya Z. Musina, Vlada K. Fediaeva, Vadim V. Tarasov

ORCID numbers: Nuriya Z. Musina 0000-0002-6914-6222; Vlada K. Fedyaeva 0000-0002-7730-1237; Vadim V. Tarasov 0000-0002-9394-7994

Correspondence to: Nuriya Z. Musina, PhD in Pharmaceutical Sciences, Associate Professor, Health Technology Assessment Specialist at the Institute of Translational Medicine and Biotechnology, Sechenov First Moscow State Medical University (Sechenov University).
Address: 8/2, Trubetskaya str., Moscow, 119048, Russia
E-mail: musina_n_z@staff.sechenov.ru

Nuria Z. Musina, PhD in Pharmaceutical Sciences, Associate Professor, Health Technology Assessment Specialist at the Institute of Translational Medicine and Biotechnology, Sechenov First Moscow State Medical University (Sechenov University), 8/2, Trubetskaya str., Moscow, 119048, Russia

Vlada K. Fediaeva, Health Technology Assessment Specialist at the Institute of Translational Medicine and Biotechnology, Sechenov First Moscow State Medical University (Sechenov University), 8/2, Trubetskaya str., Moscow, 119048, Russia

Vadim V. Tarasov, DSc in Pharmaceutical Sciences, Vice-Rector for Scientific and Technological Development, Sechenov First Moscow State Medical University (Sechenov University), 8/2, Trubetskaya str., Moscow, 119048, Russia

Contributors: Nuriya Z. Musina: contributed to conceptualization, writing original draft, review and editing. Vlada K. Fediaeva: contributed in review and editing. Vadim V. Tarasov: contributed in conceptualization, review and editing.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Informed consent statement: Not required

Funding: None

Competing interests: The authors declare no conflicts of interest

Ethical approval: Not required.

Data sharing: Not applicable.

Manuscript source: Unsolicited manuscript

Country/Territory of origin: Russia

ABSTRACT

Horizon scanning (HS) in healthcare is a strategic framework designed to identify and evaluate emerging medical technologies with the potential to significantly influence health systems. In response to rapid scientific and technological advancements, and the increasing demand for long-term forecasting, HS has been institutionalized in many settings, allowing for its integration into national healthcare planning and policy development.

International experience demonstrates that the systematic application of HS contributes significantly to evidence-based decision-making in healthcare. By enabling the timely identification and evaluation of emerging technologies, HS helps mitigate potential risks, supports proactive policy responses, and enhances the overall efficiency and responsiveness of healthcare systems.

In the Russian Federation, some HS activities are underway; however, they are not yet institutionalized, do not involve all key stakeholders, and are not supported by advanced technological platforms such as artificial intelligence or big data analytics. This limits the country's capacity for strategic foresight and long-term innovation planning in healthcare. The adoption of an integrated HS framework could substantially improve system efficiency by facilitating timely access to high-impact innovations, enhancing resource allocation, and informing evidence-based health and pharmaceutical policy. Strengthening collaboration with international organizations and BRICS partners could support the development of common methodological

Received: 07.02.2025
Accepted: 15.04.2025
Date of publication: 19.05.2025

approaches, promote shared technology assessment priorities, and reinforce collective readiness for emerging health challenges. The use of advanced analytical tools would further enable the integration of HS into national decision-making and contribute to building a resilient, proactive system for anticipating technological change.

Key Words: medical innovation; early awareness; health technologies; artificial intelligence; strategic forecasting; health technology assessment; technology trends

Citation: Musina NZ, Fedyaeva VK, Tarasov VV. From global practice to national strategy: horizon scanning tools for healthcare transformation in Russia. *The BRICS Health Journal.* 2025;2(1):13-26. https://doi.org/10.47093/3034-4700.2025.2.1.13-26

Introduction

Horizon scanning (HS) in healthcare is an essential element of strategic planning, aimed at improving access to innovative technologies and strengthening population health. HS involves systematic identification of health technologies that are new, emerging or becoming obsolete and that have the potential to effect health, health services and/or society[1]. This process helps to identify potential challenges and opportunities for the healthcare system, thereby enabling more timely and effective responses. In the context of rapid technological advancement and evolving demographic trends, early identification of factors that may affect health systems is essential. Some authors consider HS to be part of an early awareness and alert system[2], which aims to detect, filter, and prioritize new and breakthrough health technologies – or novel applications of existing ones – and to assess or predict their potential impact on health outcomes, health systems, and society. This is followed by the dissemination of relevant information to support decision-making [1].

In the 1980s, the need for a more proactive approach to managing technological innovation in HS was first articulated. It was recognized that waiting to address new technologies only after their consequences had materialized was insufficient. This led to the proposal of a structured system for the early identification and assessment of emerging health technologies – an "early warning system" – designed to inform decision-makers in advance [2]. The development of the early awareness and alert system concept progressed through a series of seminars in the Netherlands, Sweden, and Denmark during the 1990s. These seminars identified a shared interest in exchanging information about new health technologies, their evaluation, and their integration into healthcare systems. This collaborative effort led to the formal establishment of the EuroScan International Network in 1999. EuroScan is a global network that collects and shares information on emerging health technologies, supporting evidence-based decision-making and the adoption of effective and safe innovations. The network also serves as an international forum for developing methods for the early identification and assessment of new technologies and their impact on healthcare systems [1]. The activities and contributions of EuroScan will be discussed in more detail below.

HS was initially introduced as the first stage in the health technology assessment (HTA) process and was conducted by HTA agencies or aca-

[1] HTA Glossary. Horizon scanning. HTA Glossary website. Accessed 05.02.2025. https://htaglossary.net/horizon-scanning
[2] HTA Glossary. Early awareness and alert system. HTA Glossary website. Accessed 05.02.2025. https://htaglossary.net/early-awareness-and-alert-system

demic institutions to systematically evaluate the potential impact of new and emerging health technologies on healthcare systems. This approach was adopted in countries such as the United Kingdom, Sweden, Norway, France, the Netherlands, Canada, and Australia. Today, there is a clear trend toward expanding the functions of these centers, involving a broader range of stakeholders across the healthcare system, and actively integrating innovative technological platforms e.g., artificial intelligence (AI) into HS activities [3-5].

Horizon scanning tools

There is currently no universally accepted methodology for conducting HS; however, the strategies employed across countries and international organizations share common features and can be systematized[3] [4-9]. HS systems may be oriented toward either short-term (up to 5 years) or long-term (more than 5 years) horizons, which in turn influences the selection of specific methodological approaches. The key stages of the HS process include identification (signal detection), filtration, prioritization, assessment, dissemination, and ongoing updating/monitoring[4,5] [3].

The identification of health technologies is a complex process that involves the use of multiple methods. Below, we outline the most commonly applied approaches.

1. Literature reviews and analysis of scientific publications: This is the primary method used in HS, and all organizations engaged in HS activities rely on the analysis of published scientific data. This type of analysis can be further categorized into the following subtypes:
   - Bibliometric analysis: a quantitative method for analyzing scientific publications to identify emerging trends and priority areas of research and development in healthcare, with particular relevance to the pharmaceutical sector. This approach enables the detection of the most actively explored domains within medical science.
   - Systematic reviews: a structured search of clinical studies and other relevant literature (including conference and symposium abstracts), with a description of their findings. This may involve critical appraisal and, where appropriate, evidence synthesis such as meta-analyses or indirect comparisons. This type of analysis not only helps to identify innovative medical technologies but also allows for an assessment of their potential impact on patient outcomes.

   The analysis of published literature, including completed clinical trials, is among the most resource-intensive methods used in HS. Nevertheless, it provides essential inputs for subsequent health economic evaluations, such as identifying clinically relevant criteria for efficacy and safety of the technology under consideration. However, exclusive reliance on published clinical studies may result in missed opportunities to identify technologies that are still in earlier stages of development.
2. Analysis of clinical trial registries and databases: The analysis of clinical trial registries – such as ClinicalTrials.gov and other national or international platforms – allows for the early identification of ongoing and planned clinical studies involving novel health technologies. Monitoring

[3] Research Report: A Systematic Review of Methods for Health Care Technology Horizon Scanning. Content last reviewed July 2019. Effective Health Care Program, Agency for Healthcare Research and Quality, Rockville, MD. Accessed 05.02.2025. https://effectivehealthcare.ahrq.gov/products/horizon-scan/research-2013

[4] Wild, C. and Langer, T. (2006): Horizon Scanning System (HSS). An Overview. HTA-Projektbericht 02. Accessed 05.02.2025. https://eprints.aihta.at/586/

[5] Oortwijn W. Facing the dynamics of future innovation: The role of HTA, industry and health system in scanning the horizon. Accessed 05.02.2025. https://htai.org/global-policy-forums-background-papers.

these registries and tracking study outcomes supports the detection of innovations at the earliest stages of their development.

Compared to bibliometric analysis, this approach provides insights into technologies that are likely to reach market authorization over a longer-term horizon.

3. Patent database analysis: Patents are widely regarded as indicators of future technological directions, making them a valuable source of information within HS frameworks. The volume and thematic focus of patent filings can serve as predictors of which technologies are likely to become dominant in the marketplace in the coming years. For instance, the increasing number of patents related to gene and cell therapies suggests substantial future potential in these areas. Patent databases—such as those maintained by the World Intellectual Property Organization (WIPO), the United States Patent and Trademark Office (USPTO), the European Patent Office (EPO), and others – offer global coverage, which is particularly relevant for the healthcare sector operating across international markets. These resources facilitate the assessment of patentability and commercialization potential in different countries and regions.

   The analysis of patent databases enables the identification of innovative medical technologies at the earliest stages of their development.

4. Conducting expert surveys: Expert involvement in HS is possible at various stages and makes it possible not only to validate the results obtained but also to identify unmet clinical needs that may not be evident to researchers and developers of medical technologies. This contributes to more targeted HS , focused on addressing specific medical challenges, and also enables HS institutions to set priorities more effectively.

   At the same time, validation of HS results is critically important, as clinical experts are best positioned to assess whether new developments and technologies will be applicable in real-world clinical settings. They can also determine which innovations have the highest potential for successful integration into clinical practice, taking into account national and regional specificities – thus improving the likelihood of their commercialization and acceptance by physicians and patients.

   Expert surveys may be conducted using the following methods:

   - Delphi method: collection of expert opinions through a series of questionnaires, enabling consensus on the potential value of a new medical technology for the healthcare system.
   - Focus groups and strategic sessions: organized discussions with healthcare professionals (clinicians, health administrators, etc.), scientists, researchers, and industry representatives to gather information on new technologies and assess their potential significance for the system.

5. Technology scouting and market analysis: Technology scouting involves the active search for new health technologies within universities, research institutions, biotechnology companies, and startups. This enables early identification of potential technological breakthroughs that may significantly impact the healthcare sector. Technology scouting supports informed investment decisions by assessing which innovations hold the greatest potential to improve clinical practice and expand access to healthcare services.

   The analysis of published market reports, future market projections, and investment trends allows for the evaluation of a product's potential commercial success, its alignment with the existing ecosystem, and the anticipated costs associated with its market introduction.

These tools help forecast challenges associated with the implementation of innovation. Market analysis can identify barriers to market entry, such as regulatory constraints, integration challenges within existing healthcare infrastructure, or limited demand for certain technologies. Technology scouting, in turn, can highlight technological risks – for example, a lack of readiness for large-scale application or unresolved concerns regarding safety and effectiveness during the development phase.

6. Monitoring regulatory agencies for health technology approvals: Monitoring the activities of regulatory agencies – such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and others—is also an important element of HS, as it allows for tracking new approvals and market authorization applications for health technologies. In addition, the analysis of reports from international regulators enables companies and research organizations to plan their development strategies more effectively and minimize risks by considering existing regulatory guidance. It also helps anticipate changes in the sector and supports more informed decision-making in the development and commercialization of health technologies.
7. Building partnerships across healthcare systems: Establishing partnerships with all key stakeholders in the healthcare system is essential to strengthening HS activities and ensuring their relevance to real-world needs. Patient organizations, in particular, play a critical role in identifying unmet medical needs and providing insight into technologies currently in use in clinical practice. Their input helps align HS efforts with the actual experiences and priorities of patients.

   The healthcare industry also serves as an important partner, offering early access to information about technologies under development. Companies can contribute insights into innovations at various stages of the research and development (R&D) pipeline –from preclinical concepts to late-stage products – thereby supporting more accurate forecasting and timely assessment. Collaboration with industry stakeholders enhances the comprehensiveness of HS and enables proactive engagement with technologies well before they reach regulatory review or market authorization.

   Involving academia, regulators, payers, healthcare providers, and professional associations further reinforces the HS ecosystem, facilitating the triangulation of evidence, validation of findings, and alignment with broader health system goals.
8. Data mining and use of AI: AI and digital technologies are playing an increasingly important role in HS processes. They enable the processing of vast volumes of data and the identification of hidden trends, thereby improving the overall efficiency of HS. Big data analytics significantly enhances the effectiveness of HS by automating routine tasks, allowing real-time analysis of data from diverse sources, and applying machine learning algorithms to detect latent patterns and trends, as well as to forecast future developments based on historical data.

   Machine learning plays a central role in data analysis and the prediction of technological trends. The main machine learning methods used in HS include:
   - Supervised learning – the use of labeled datasets to train models for predicting future events;
   - Neural networks – the use of multilayer neural architectures to analyze complex data, enabling classification and clustering (i.e., grouping data based on shared characteristics and uncovering hidden patterns);

- Natural language processing – technologies that allow automated analysis of textual information from various sources, such as scientific publications, patents, and news outlets.

9. Scenario planning and trend analysis: Scenario planning is a comprehensive process that enables the modeling and evaluation of various possible future developments and the associated risks, based on key trends and uncertainty factors such as shifting epidemiological patterns, economic dynamics, regulatory changes, and more. It is typically conducted in the form of foresight sessions involving multidisciplinary experts, including representatives from regulatory bodies and patient organizations.

   Scenario planning incorporates trend analysis, which involves the study of broad, long-term, and global shifts that impact demographics and the healthcare system as a whole.

   Within the context of HS, scenario planning helps healthcare stakeholders prepare for an uncertain future by exploring different possible trajectories. This tool enables companies, public institutions, and research organizations to develop flexible strategies, reduce risk, and make more informed decisions – ultimately facilitating the successful adoption of innovation and the long-term strengthening of the healthcare system.
10. Monitoring conferences and exhibitions: Attending and monitoring presentations and posters at major scientific conferences, as well as participating in trade and industry exhibitions, can also be valuable for identifying research activities and the development of new health technologies.

Naturally, determining an effective strategy for the identification of new health technologies requires the use of a combination of methods in each specific case. The value of each method varies depending on the objectives and focus of HS (for example, the area of interest may be limited to pharmaceuticals, surgical interventions, or diagnostic methods). To assess the appropriateness and value of specific methods, as well as to evaluate and aggregate HS results, tools such as multi-criteria decision analysis may be applied [10, 11].

The next stages of HS include the filtration and prioritization of health technologies. Filtration may be conducted according to a range of criteria, including: the effectiveness of the technology, the size of the target patient population (expected to be affected by the technology), degree of innovation, availability of current alternatives, disease severity, strength of evidence on efficacy and safety, organizational impact, alignment with healthcare policy priorities, development stage, feasibility, ethical and social implications, and expected time to implementation. HS typically considers a time horizon of 2–15 years. This reflects the fact that technologies expected to have an impact within less than 2 years are often already in late stages of development, while forecasts beyond 15–20 years tend to be too distant and uncertain to be actionable.

Technologies selected through filtration are subsequently prioritized (i.e., ranked based on their relevance to the healthcare system). Prioritization methods may include both qualitative and quantitative approaches, scoring and ranking, risk analysis, the Delphi method, public consultations, and expert involvement. The aim of prioritization is to select technologies based on their potential clinical and economic impact, as well as other predefined criteria [5].

Impact assessment may be conducted as a rapid analysis or as an in-depth evaluation that incorporates both clinical and economic aspects. The assessment includes forecasting the adoption of technologies, evaluating their impact on clinical outcomes, infrastructure, and costs, as well as analyzing potential ethical and social implications.

Dissemination of information includes the publication of electronic and print reports, the creation and maintenance of databases on emerging technologies, and the preparation of regular informational bulletins.

National models and institutional approaches to horizon scanning in healthcare

In many countries, HS in healthcare is carried out within the framework of HTA agencies and tends to be fragmented, focusing primarily on evaluating the potential impact of new technologies on reimbursement systems. The time horizon is typically limited to no more than 5 years [12].

Italy [13] serves as a prominent example, where since 2006 a structured short-term HS program has been implemented to monitor the emergence of new medicinal products and to provide the national regulator the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) with information at three key stages – 36, 18, and 12 months prior to expected EMA market authorization. While this system supports early preparedness and resource planning, it is narrowly focused on pharmaceuticals and technologies close to market entry.

Similar models are in place in Norway, Sweden, the Netherlands, France, Australia, Canada, New Zealand, and South Korea [9, 12, 14].

Unlike many other countries, the United Kingdom [15] has developed a more centralized approach to HS that is embedded within the structure of the National Health Service (NHS).

The National Institute for Health and Care Research (NIHR) Innovation Observatory[6], operating under the NHS and hosted by Newcastle University, plays a pivotal role in HS by informing healthcare policy, regulation, and research strategy. The Observatory monitors future pharmaceuticals, medical devices, and diagnostic technologies starting from the patent stage, often up to ten years before potential clinical adoption. The early identification of new health technologies typically begins three years prior to expected market authorization, aiming to compile data 24–30 months before anticipated launch. For novel medicines and advanced therapies, HS reports are generated 20 months before the expected marketing authorization, and 15 months in advance for new indications of already approved products. The Observatory's core areas of activity include:

- HS and analytics: it systematically identifies and analyzes scientific and technological trends using diverse data sources, such as scientific literature, patents, and market intelligence. The Observatory also engages patient organizations and clinical experts to improve the relevance of its forecasts. Two primary approaches are used: general routine "horizontal scanning" and in-depth thematic reviews in clinical areas with known unmet needs or high healthcare demand.
- Assessment and recommendations: based on collected evidence, the Innovation Observatory evaluates the potential benefits and risks of emerging technologies. The resulting recommendations support decision-making by government bodies, industry, and academic institutions regarding the adoption and advancement of innovations.
- Support for research and development: the Observatory collaborates with universities, research institutes, and commercial partners, providing access to data and insights that guide the development of new products and technologies, ranging from basic science to applied innovation.
- Education and knowledge dissemination: through training programs, workshops, and conferences, the Innovation Observatory raises aware-

[6] NIHR Innovation Observatory. Newcastle upon Tyne: NIHR Innovation Observatory. Accessed 05.02.2025. https://io.nihr.ac.uk/

ness and understanding of new technologies among stakeholders, helping to foster an innovation-ready ecosystem.
- Strategic planning and policy development: drawing on its data and analytics, the Observatory contributes to long-term strategic planning and the formulation of policy recommendations aimed at strengthening innovation systems at both regional and national levels.

The Observatory also offers access to tools, databases, reports, and dashboards developed through its programs to support translational research[7]. This enables researchers and developers to apply cutting-edge methods and evidence to accelerate the integration of innovations into clinical practice.

Brazil was the first among BRICS countries to take steps toward the systematic implementation of HS in healthcare. In 2011, the National Committee for Health Technology Incorporation (CONITEC) was established, and beginning in 2014, in collaboration with scientific institutions, it began developing HS mechanisms for the early identification of new health technologies with potential impact on the national Unified Health System (SUS). Between 2014 and 2018, CONITEC developed and introduced various analytical tools, including internal reports, early alerts, and briefing documents on emerging technologies. These materials became an important resource for informing healthcare authorities and supporting decisions regarding the incorporation of new technologies into the healthcare system [16].

One of the key milestones was the launch of the RADAR platform in 2014, designed to disseminate analytical information on novel and emerging technologies. Developed by the Ministry of Health in collaboration with other institutions, the platform enabled timely communication with the medical community about technological changes, contributing to greater transparency and proactive innovation management in healthcare [17].

Brazil's experience demonstrates that institutionalizing HS within the national regulatory framework not only facilitates the evaluation of promising technologies but also supports their managed introduction – helping ensure the sustainability of the system in a rapidly evolving technological landscape. According to publicly available data, HS in other BRICS countries is not institutionalized and is not carried out on a regular or systematic basis. Unlike Brazil, where HS is integrated into national health governance, in India, China, Russia, South Africa, and the UAE, HS-related activities are conducted within isolated research projects or by individual institutions. To date, none of these countries have established centralized national mechanisms for the continuous identification and assessment of emerging health technologies.

International organizations and initiatives in horizon scanning

World Health Organization

The World Health Organization (WHO) plays an active role in international HS initiatives. The Global Health Futures Forum brings together experts to discuss future challenges and opportunities in healthcare. Its key areas of focus include conducting research and analyzing future health trends, coordinating efforts and sharing experiences across countries, and developing strategic planning and innovation implementation recommendations for WHO Member States [18].

[7] ScanMedicine. Accessed 01.02.2025. https://www.scanmedicine.com/

Organisation for Economic Co-operation and Development

The Organisation for Economic Co-operation and Development (OECD) actively engages in HS initiatives within the healthcare sector. Through its Strategic Foresight unit, the OECD employs HS to systematically detect early signs of potentially significant developments, particularly in science and technology, to anticipate their future impacts on healthcare systems[8].

In its 2017 report, "New Health Technologies: Managing Access, Value and Sustainability," the OECD reviewed various technology foresight and HS studies. The report highlighted the importance of these methodologies in identifying emerging technologies likely to transform healthcare within the next five to ten years. It also discussed national initiatives in HS, emphasizing the role of such activities in preparing health systems for new technological advancements [19].

Furthermore, the OECD has developed frameworks for anticipatory governance of emerging technologies, advocating for the use of robust tools such as HS, advanced data analytics, forecasting, and technology assessment. These tools are employed to anticipate future developments and inform policy-making processes, ensuring that health systems are equipped to manage upcoming innovations effectively[9].

As noted above, EuroScan [3] brings together organizations engaged in HS to improve methodologies and facilitate the exchange of information on emerging and new health technologies, thereby supporting the faster adoption of effective innovations across countries. Despite its name, the network includes members from around the world, including Brazil, Malaysia, Canada, Australia, and others, fostering the exchange of best practices and analytical approaches. EuroScan focuses primarily on ensuring access to up-to-date information to support decision-making, mitigate risks, and optimize resource allocation in healthcare. The organization employs both proactive and reactive monitoring strategies, including surveillance of scientific literature, patent activity, and clinical trial data. EuroScan also works actively with regulators and stakeholders, adapting implementation approaches and promoting the sustainable integration of innovation into health systems.

International horizon scanning initiative

The International Horizon Scanning Initiative (IHSI)[10] was established in 2019 as an independent organization that delivers early intelligence on emerging pharmaceutical innovations to its participating countries. The initiative originated from the Beneluxa collaboration – a cross-border alliance in healthcare involving Belgium, the Netherlands, Luxembourg, Austria, and Ireland – yet IHSI functions independently, enabling countries to join without being part of Beneluxa. Initial IHSI members included Belgium, the Netherlands, Denmark, Ireland, Norway, Portugal, Sweden, and Switzerland, with several other countries expressing interest in participation.

The IHSI model, developed by the Belgian Health Care Knowledge Centre (KCE), involves the systematic identification and assessment of medicines expected to significantly impact healthcare systems. The central implementation unit produces high-impact reports and maintains a

[8] Organisation for Economic Co-operation and Development (OECD). Strategic foresight. Accessed 03.02.2025. https://www.oecd.org/en/about/programmes/ strategic-foresight.html

[9] OECD. Strategic Foresight. OECD website. Accessed 04.02.2025. https://www.oecd.org/strategic-foresight/

[10] International Horizon Scanning Initiative (IHSI). Horizon scanning system. IHSI website. Accessed 05.02.2025. https://ihsi-health.org/horizon-scanning-system/

shared database that supports decision-making on pricing, reimbursement, budget planning, and access strategies. These outputs are directly used by national health authorities and payers to anticipate clinical and financial consequences of new therapies and to align healthcare system readiness with innovation trajectories.

IHSI represents a strong example of how countries can pool resources and expertise to conduct structured, forward-looking HS that directly informs national health policy. Its model offers a useful reference for BRICS countries, which could benefit from establishing a joint HS platform to monitor global pharmaceutical developments, strengthen local decision-making capacity, and support regional innovation planning and access strategies.

Horizon scanning in the Russian healthcare system: current gaps and strategic needs

At present, a systemic HS process has not been widely adopted in the Russian healthcare system. In contrast to advanced international practices—where HS is actively employed to anticipate change and guide healthcare systems in adapting to future challenges – Russia has yet to integrate this tool at the national level. This hampers the ability to account for long-term trends and potential technological breakthroughs in decision-making and planning.

Although a national HTA framework was introduced in 2014, it remains largely reactive. Assessments are typically initiated by applicants—primarily pharmaceutical companies – and individual technologies are reviewed only at the request of the Ministry of Health or affiliated scientific institutions[11]. This case-by-case approach does not enable comprehensive or continuous monitoring of innovation. Moreover, the current HTA horizon is typically limited to 2–3 years and focused on specific diseases, which restricts strategic foresight and limits the healthcare system's preparedness for transformative advances.

In recent years, several initiatives have been launched to support the identification and evaluation of innovative technologies. Two centers dedicated to medical technology transfer and coordination of biomedical research were established in 2022 under a federal program aimed at advancing medical science. Additionally, a national information system was introduced to collect and store data on publicly funded R&D projects conducted by institutions subordinate to the Ministry of Health [*7*].

However, these efforts do not constitute a systemic HS process. First, they are narrowly focused on the internal needs of public institutions and are not designed to provide early intelligence across the full spectrum of emerging health technologies. Second, these mechanisms operate in isolation and are not embedded within a continuous, transparent, and coordinated national foresight framework. There is no structured methodology for technology prioritisation, no regular scanning cycles, and no active engagement of key stakeholders such as industry, academic researchers, patients, or payers. In addition, these initiatives do not leverage modern analytical platforms such as AI, big data analytics, or predictive modelling. To be effective, HS must rely on these technological tools and be integrated into a national-level framework that ensures collaboration across all sectors of the healthcare and innovation ecosystem.

[11] Government Decree No. 871 of August 28, 2014. On the procedure for the development of lists of medicinal products for medical use and the minimum assortment of medicines needed for medical care provision. Accessed 05.02.2025. http://government.ru/docs/14540/

At the same time, other sectors in Russia are already successfully using sophisticated forecasting systems. One notable example is iFORA (Intelligent Foresight Analytics), an intelligent foresight analytics platform developed by the Institute for Statistical Studies and Economics of Knowledge at the National Research University Higher School of Economics. This system uses big data analytics, machine learning, and semantic technologies to identify major technological and economic trends and forecast the development trajectories of various sectors[12]. Applying such advanced analytical tools in healthcare – adapted to sector-specific needs—could significantly enhance governance and strategic planning. It would also support the establishment of a unified, sustainable, and forward-looking HS process.

HS in healthcare is a strategic instrument for identifying and evaluating future trends and potential shifts that may affect the health system. Its implementation could bring substantial benefits for Russia:

- Strategic planning: enables early identification of long-term trends and potential challenges, allowing for the development of proactive policies, innovation strategies, and better resource allocation. This improves system readiness and strengthens the competitiveness of sectors such as healthcare, pharmaceuticals, and biotechnology.
- R&D: supports the identification of priority areas for investment, encourages collaboration between academic institutions and industry, and contributes to the planning of joint scientific initiatives.
- Export potential: enhances the global competitiveness of Russian health technologies by continuously monitoring healthcare systems abroad, including regulatory requirements, reimbursement frameworks, clinical practice trends, and unmet medical needs.
- Policy development: facilitates timely adjustments to health and pharmaceutical policy through evidence-informed regulation and supports faster, safer integration of innovations into clinical practice.
- Informed funding decisions: provides a robust evidence base to guide public and private investment in high-impact technologies, improving the alignment of financial decisions with system and patient needs.
- Early access to innovation: improves system preparedness for the introduction of emerging health technologies, reducing time to implementation and increasing adoption efficiency.
- Healthcare cost management: identifies technologies that enhance diagnostic and therapeutic efficiency, reduce long-term system costs, and inform future planning for medical infrastructure and supply needs.
- Support for HTA: provides early-stage data and insights on new and emerging health technologies, enabling HTA bodies to conduct more comprehensive, timely, and informed evaluations of clinical effectiveness, safety, and economic impact.
- Patient benefit: enables quicker access to innovative treatments, supports improved health outcomes, and contributes to the advancement of personalized medicine approaches.
- Risk management: anticipates systemic and technological risks and supports the development of early mitigation strategies, contributing to greater resilience and sustainability of the healthcare system.

International experience shows that the results of HS have a wide range of potential users [1, 5, 8], making it particularly important to ensure broad dissemination of HS outputs and access to information for all interested stakeholders. In the context of the Russian Federation, potential users of HS results in healthcare may include:

[12] Institute for Statistical Studies and Economics of Knowledge. iFORA: Intelligent Foresight Analytics System. Moscow: HSE University. Accessed 01.02.2025. https://issek.hse.ru/en/ifora/u

- Research institutions and academic centers: can use HS to identify emerging research priorities and align scientific agendas with the future needs of the healthcare system. This helps direct efforts toward high-potential areas for the development of new health technologies.
- Pharmaceutical companies and manufacturers of health technologies: may rely on HS to better understand long-term national priorities, assess the market potential of their innovations, and optimise development strategies. Early access to strategic intelligence supports more efficient product planning and commercialization.
- Healthcare providers (e.g. hospitals and clinics): use HS to identify, evaluate, and adopt innovative diagnostic and therapeutic solutions. This enables timely integration of new technologies into clinical practice and contributes to improving the quality and efficiency of care delivery.
- Patient organizations: benefit from early awareness of upcoming treatment options and technological innovations. HS also enables stronger engagement in policy development and participation in clinical research and advocacy.
- Health insurers and payers, including the Mandatory Health Insurance Fund: use HS to evaluate the potential impact of new technologies on clinical outcomes and healthcare budgets. This supports evidence-informed reimbursement decisions and long-term financial planning.
- Venture capital firms and institutional investors: use HS to identify promising areas for investment in biomedical and health technology innovation. Access to early signals reduces investment risks and helps prioritize resources for high-impact technologies.
- Regulatory authorities: draw on HS findings to anticipate future regulatory needs, adapt evaluation frameworks, and accelerate the review and approval of transformative health technologies.
- HTA agencies: use HS to prepare for upcoming submissions, collect early data on safety, clinical effectiveness, and cost-effectiveness, and enhance the quality and relevance of assessments.
- Government ministries and policy-makers: the Ministry of Health can use HS to anticipate public health needs, plan national program, and allocate resources more effectively. Early awareness of pipeline innovations is crucial for timely decision-making on access and financing. The Ministry of Industry and Trade can use HS to guide industrial strategy by aligning domestic production with projected healthcare demands and global technology trends.

Importantly, the development of an effective HS framework should also include mechanisms for international cooperation – particularly within strategic alliances such as BRICS. Collaboration with BRICS partners can facilitate joint foresight studies, the exchange of early intelligence on emerging health technologies, coordination of research priorities, and cross-border innovation planning. Such efforts can strengthen the collective preparedness of BRICS health systems, enhance industrial integration, and create a shared vision for navigating global health technology transitions.

To unlock these benefits, Russia must move beyond isolated initiatives and establish a unified, institutionalized HS framework for healthcare. This should be forward-looking, technologically advanced, inclusive of all system stakeholders, internationally coordinated, and aligned with broader socioeconomic and industrial strategies.

Conclusion

In an era of rapid advances in medical science and technology—paired with the financial constraints faced by healthcare systems – HS has be-

come a critical tool for identifying and evaluating developments that may shape the future of health systems. By applying modern analytical methods and digital technologies, HS enables not only reactive adaptation to emerging trends but also proactive shaping of healthcare futures.

The results of HS can have far-reaching policy implications. They support the formulation of national health priorities, guide strategic investment in research and development, inform the design of legal and regulatory frameworks, and define focal points for international cooperation. For example, HS findings can recommend closer collaboration with specific international partners around shared research agendas or priority technologies. Importantly, all stakeholders within the healthcare system are potential users of HS outputs and should be actively engaged in their dissemination and application.

In the context of international integration, collaboration within BRICS countries is especially important. Joint efforts in HS could strengthen the collective ability to monitor health technologies and enhance the quality of strategic forecasting. For Russia, systematic work in HS is particularly relevant to ensure early identification of technology trends, develop a consistent regulatory framework with aligned innovation policy. Coordinated initiatives would not only improve the identification of global technology trends, but also support the alignment of innovation policy, regulatory strategy, and implementation across diverse health systems.

References

1. Packer C, Gutierrez-Ibarluzea I, Simpson S. The evolution of early awareness and alert methods and systems. *Int J Technol Assess Health Care.* 2012 Jul; 28(3):199-200. doi:10.1017/S0266462312000426.
2. Banta HD, Gelijns AC. The future and health care technology: implications of a system for early identification. *World Health Stat Q.* 1994;47(3-4):140-8.
3. Simpson S., Hiller J., Gutierrez-Ibarluzea I., Kearney B., Norderhaug I., Fay AF., et al. A toolkit for the identification and assessment of new and emerging health technologies 2014. *EuroScan International Network.* 2014. doi:10.13140/RG.2.1.4206.0645.
4. Vignali V, Hines PA, Cruz AG, et al. Health horizons: Future trends and technologies from the European Medicines Agency's horizon scanning collaborations. Front Med (Lausanne). 2022;9:1064003. doi:10.3389/fmed.2022.1064003.
5. Hines P, Hiu Yu L, Guy RH, et al. Scanning the horizon: a systematic literature review of methodologies. *BMJ Open.* 2019 May 27;9(5):e026764. doi:10.1136/bmjopen-2018-026764.
6. National Academies of Sciences, Engineering, and Medicine, et al. Horizon Scanning and Foresight Methods. In: *Safeguarding the Bioeconomy.* Washington (DC): National Academies Press (US); 2020. doi:10.17226/25525.
7. Soon JA, To YH, Alexander M, et al. A tailored approach to horizon scanning for cancer medicines. *J Cancer Policy*. 2023;38:100441. doi:10.1016/j.jcpo.2023.100441.
8. Ягудина РИ, Куликов ВА. Сканирование горизонтов, как инструмент для информирования регуляторов здравоохранения об инновационных технологиях. Современная организация лекарственного обеспечения. / Yagudina RI, Kulikov VA. Horizon scanning as a tool to inform healthcare regulators about innovative technologies. *Sovremennaya Organizatsiya Lekarstvennogo Obespecheniya = Modern organization of drug supply. 2019; 6 (3):5-10. (In Russian).*
9. Омельяновский ВВ, Мухортова ПА, Зинадинов СИ, и др. Опыт применения систем сканирования горизонтов для выявления инновационных технологий здравоохранения в различных странах мира. *Трансляционная медицина. /* Omelyanovskiy VV, Mukhortova PA, Zinadinov SI, et al. International experience in

the application of horizon scanning systems for identifying innovative health technologies. *Transl Med*. (In Russian). 2024;11(6):546–561. doi:10.18705/2311-4495-2024-11-6-546-561.
10. Ruggeri M, Cadeddu C, Roazzi P, et al. Multi-Criteria-Decision-Analysis (MCDA) for the Horizon Scanning of Health Innovations an Application to COVID 19 Emergency. *Int J Environ Res Public Health*. 2020;17(21):7823. doi:10.3390/ijerph17217823.
11. Smith J, Cook A, Packer C. Evaluation criteria to assess the value of identification sources for horizon scanning. *Int J Technol Assess Health Care*. 2010;26(3):348-353. doi:10.1017/S026646231000036X.
12. Vogler S. "Ready for the future?" – Status of national and cross-country horizon scanning systems for medicines in European countries. *Ger Med Sci.* 2022 Mar 31;20:Doc05. doi: 10.3205/000307.
13. Joppi R, Demattè L, Menti AM, et al. The Italian Horizon Scanning Project. *Eur J Clin Pharmacol.* 2009;65(8):775-81. doi:10.1007/s00228-009-0666-z.
14. Ormstad SS, Wild C, Erdös J, Moulton K. Mapping horizon scanning systems for medical devices: similarities, differences, and lessons learned. *Int J Technol Assess Health Care*. 2023;39(1):e69. doi:10.1017/S0266462323002684.
15. Khan S, Fairbairn R, Potter R, Hussain A, Inskip A, Norman G. Horizon scanning methods for identification of new and repurposed medicines for stakeholders in the United Kingdom. *Front Pharmacol.* 2022;13:938508. doi:10.1002/ffo2.210.
16. Gomes PTC, Mata VE, Borges TC, Galato D. Horizon scanning in Brazil: outputs and repercussions. *Rev Saude Publica*. 2019;53:111. doi:10.11606/S1518-8787.2019053001439 .
17. Gomes PT, Teixera Vidal A, Souza A. Radar – An Important Tool for Horizon Scanning Dissemination in Brazil. *Value Heal.* 2017;20(9):PA906. doi: 10.1016/j.jval.2017.08.2787.
18. Kemp L, Ilchmann K, Rajatonirina S, et al. Emerging technologies and dual-use concerns: a horizon scan for global public health. *Bulletin of the World Health Organization.* 2021. ISBN 9789240036161
19. OECD. *New Health Technologies: Managing Access, Value and Sustainability.* Paris: OECD Publishing. 2017. doi:10.1787/9789264266438-en.

The BRICS HEALTH JOURNAL 2025; 2 (1): 27–37

journal homepage: https://www.bricshealthjournal.com
https://doi.org/10.47093/3034-4700.2025.2.1.27-37

REVIEW

Ayushman Arogya Mandir: a revolutionary primary healthcare approach shaping India's path to universal health coverage

Aradhana Patnaik, Atul Kotwal, Harsh Mangla, Jyoti Rai

Aradhana Patnaik, Additional Secretary and Mission Director, National Health Mission, Ministry of Health and Family Welfare, New Delhi – 110011, India

Atul Kotwal, Executive Director, National Health Systems Resource Centre Baba Gangnath Marg, Munirka, New Delhi – 110067, India

Harsh Mangla, Director, National Health Mission, Ministry of Health and Family Welfare, New Delhi – 110011, India

Jyoti Rai, Sr. Consultant, Ministry of Health and Family Welfare, New Delhi – 110011, India

ABSTRACT

The Ayushman Arogya Mandir (AAM) initiative is a transformative approach in India's journey towards Universal Health Coverage (UHC), addressing long-term deficiencies in the primary healthcare system. Launched in April 2018 under the Ayushman Bharat program, AAM seeks to revolutionize primary healthcare by upgrading existing Sub Health Centres and Primary Health Centres to provide comprehensive, free of cost services spanning preventive, promotive, curative, rehabilitative, and palliative care. This strategic shift has significantly improved access, particularly in underserved and rural areas. By integrating expanded range of services including non-communicable diseases (NCDs) and mental health into primary care, and by enhancing community mobilization and promotion, AAM has made substantial strides through improved population coverage, significant reductions in Out-Of-Pocket Expenditure, and enhanced screenings for common NCDs. However, challenges persist, including infrastructural inadequacies, workforce shortages, quality of health care, information technology systems and more. Future efforts must focus on addressing these gaps through improved infrastructure, robust training programs, and advanced health information technologies. Continued research and strategic policy adjustments are also crucial to sustaining and expanding the achievements of the AAM initiative, ultimately advancing India's efforts towards UHC.

ORCID numbers: Aradhana Patnaik 0009-0006-7800-2526; Atul Kotwal 0000-0003-4592-7814; Harsh Mangla 0009-0009-3147-5096; Jyoti Rai 0009-0007-5204-0249

Correspondence to: Aradhana Patnaik, Additional Secretary and Mission Director, National Health Mission, Ministry of Health and Family Welfare.
Address: Nirman Bhavan, New Delhi – 110011, India.
E-mail: asmd-mohfw@nic.in

Contributors: Aradhana Patnaik: Conceptualization, Supervision. Atul Kotwal: Writing original draft, Formal analysis. Harsh Mangla: Writing review and editing. Jyoti Rai: Visualization. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Informed consent statement: Not required

Funding: None

Competing interests: The authors declare no conflict of interest.

Ethical approval: Not required

Data sharing: The data that support the findings of this study are available from the corresponding author (Aradhana Patnaik) upon reasonable request.

Acknowledgments: The authors are grateful to Shri Apurva Chandra for his help and support at all stages of the work.

Manuscript source: Unsolicited manuscript

Country/Territory of origin: India

Received: 26.07.2024
Accepted: 25.02.2025
Date of publication: 19.05.2025

Key Words: Primary healthcare system; Ayushman Bharat program; non-communicable diseases; out- of-pocket expenditure; community mobilization

Citation: Patnaik A, Kotwal A, Mangla H, Rai J. Ayushman Arogya Mandir: a revolutionary primary healthcare approach shaping India's path to universal health coverage. *The BRICS Health Journal.* 2025;2(1):27-37. https://doi.org/10.47093/3034-4700.2025.2.1.27-37

Introduction

India's commitment to Universal Health Coverage (UHC) has been a longstanding and progressively evolving initiative, marked by a series of strategic policies and programmatic interventions. The nation has consistently demonstrated its sustained commitment by being a signatory to the Alma Ata Declaration[1] in 1978, and more recently, signing the Astana declaration [1] in 2018. India alike other similarly placed countries, had limited focus on only reproductive and child health related services in primary health care. The selective approach was adopted in taking the geography specific health challenges.

The saturation approach was felt as need of the time. This background paved the way for integration of UHC principles into the National Health Policy 2017[2] which demonstrated a fundamental shift in India's healthcare strategy, addressing evolving health system priorities after a 15-year gap. The policy advocated for comprehensive primary healthcare, integrating services beyond Reproductive and child health to include chronic and non-communicable diseases, with referral linkages to higher facilities and ensuring continuum of care. By emphasizing higher resource allocation to primary care, the policy aimed to strengthen primary health with a focus on the vulnerable population in both rural and urban areas. For converting the vision into action, Government of India's flagship program, Ayushman Bharat was launched in 2018.

Ayushman Bharat has four main components:

1. Ayushman Arogya Mandir (AAM)[3], erstwhile Ayushman Bharat Health and Wellness Centre, to deliver comprehensive primary healthcare through strengthening and upgradation of existing primary healthcare facilities i.e. Sub Health Centre (SHC) and Primary Health Centre (PHC) in rural and urban areas;
2. Ayushman Bharat Pradhan Mantri Jan Arogya Yojana[4] to provide financial protection to cover poor and most vulnerable individuals in the country for secondary and tertiary care;
3. Ayushman Bharat Digital Mission (ABDM)[5] to ensure access, equity and continuum of care while leveraging information technology and supporting existing health systems in a 'citizen-centric' approach; and
4. Pradhan Mantri Health Infrastructure Mission[6], the country's largest pan India infrastructure scheme to develop capacity across all levels of care.

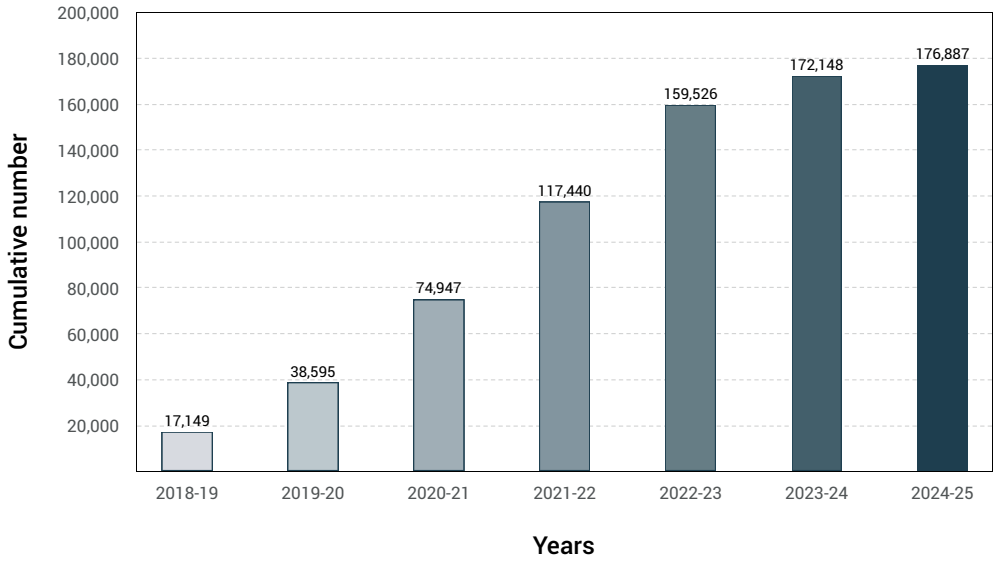
[1] World Health Organization. Regional Office for Europe. Declaration of Alma-Ata 1978. World Health Organization website. Published 08.10.2019. Accessed 27.07.2024.. https://www.who.int/publications/i/item/WHO-EURO-1978-3938-43697-61471
[2] Ministry of Health and Family Welfare. Government of India, National health policy. Published 2017. Accessed 27.07.2024. https://mohfw.gov.in/sites/default/files/9147562941489753121.pdf
[3] Government of India, Ministry of Health and Family Welfare. Ayushman Arogya Mandir website. Updated 11.12.2019. Accessed July 27, 2024. https://ab-hwc-dev.inroad.in/
[4] National Health Authority. About Pradhan Mantri Jan Arogya Yojana (PM-JAY). National Health Authority website. Accessed 27.07.2024. https://nha.gov.in/PM-JAY
[5] National Health Authority. Ayushman Bharat Digital Mission website. Accessed 27.07.2024. https://abdm.gov.in

India's health care system is three-tiered with primary health care as the first level of care, typically the first point of contact between citizens and healthcare system, catering to most of the preventive and basic curative health care needs such as SHCs & PHCs. Second tier comprises of the first referral centres providing specialist care, operative services, emergency and critical care, blood transfusion services etc. such as District Hospital (DH) & Community Health Centre, followed by tertiary level of health care for complex diagnostic procedures and treatment modalities acting as institutions for imparting education and research such as medical colleges. As per established norms[7], a PHC and SHC in rural areas is to be established for a population of 30,000 in plains (20,000 in hilly and tribal areas) and 5,000 in plains (3000 in hilly and tribal area) respectively. Similarly, PHC in urban areas are established for every 50,000 population with SHC for every 15,000 to 20,000 population in close proximity to urban slums.

The AAM initiative was announced with the aim to revolutionize primary healthcare delivery in India by transforming existing healthcare facilities i.e. SHC and PHC into AAM-SHC and AAM-PHC to address critical systemic challenges adversely affecting the Indian health system since decades. As an attempt to move from a selective to a comprehensive approach, the AAM delivers an expanded range of services spanning preventive, promotive, curative, rehabilitative and palliative care across diverse demographic and geographic landscapes, free of cost. Since its launch in April 2018, a total of 176,887 AAM have been operationalized as of March 2025 delivering primary healthcare services across the country, particularly in underserved areas (fig. 1)[8].

This article focuses on comprehensive overview of the AAM initiative, detailing its key reforms, achievements, challenges, and future directions. It will specifically elucidate India's efforts in fortifying the primary healthcare system and advancing UHC, highlighting the impact and evolution of these initiatives in improving health outcomes and achieving health equity.

FIG. 1. Year wise cumulative number of Ayushman Arogya Mandir operationalized



[6] National Health Mission. Pradhan Mantri – Ayushman Bharat Health Infrastructure Mission. National Health Systems Resource Centre website. Accessed 27.07.2024. https://nhsrcindia.org/pradhan-mantri-aatmanirbhar-swasthya-bharat-pm-asby

[7] Indian Public Health Standards Guidelines 2022. National Health Mission. Accessed 09.05.2025. https://nhm.gov.in/index1.php?lang=1&level=2&sublinkid=971&lid=154

[8] Government of India, Ministry of Health and Family Welfare. Ayushman Arogya Mandir website. Updated 11.12.2019. Accessed 27.07.2024. https://ab-hwc-dev.inroad.in/

Key reforms under Ayushman Arogya Mandir

Infrastructure development

The AAM initiative prioritizes the enhancement of existing SHC and PHC across the nation ensuring that the upgraded facilities, i.e. the AAM-SHC and AAM-PHC are well-equipped to deliver a comprehensive range of services. These enhancements encompass the construction of new buildings, renovation of existing structures, and provision of essential equipment and supplies in accordance with Indian Public Health Standard guidelines[9]. Since the announcement of the scheme, the upgradation of infrastructure coupled with quality certification, adequate sanitization and hygiene practices has been instrumental in the effective implementation of the initiative.

Expanded service delivery

The upgraded facilities now offer an expanded range of 12 services in addition to maternal and child health, addressing the increasing burden of non-communicable diseases such as diabetes, hypertension, cardiovascular diseases, and three common cancers (oral, breast, and cervical) which require long-term management. Currently, 681 million patients are enrolled under the NCD programme of the country and it is progressing well. Historically neglected mental health services are now integrated into primary care, ensuring early detection and start of treatment. In the year 2022, toll free tele mental health assistance (Tele Mental Health Assistance and Networking Across State – Tele MANAS) initiative has been rolled out pan India with more than 2.1 million calls made till date. Additionally, AAM provide services related to ENT care, eye care, oral health, trauma care, geriatric and palliative care, catering to diverse healthcare needs within the community.

Expanded human resources

The introduction of Community Health Officer represents a strategic move to strengthen the healthcare workforce in the primary healthcare system [2]. Community Health Officers (CHOs) are trained professionals managing the AAM-SHCs as the leader of the primary healthcare team, providing clinical and public health services. In addition to managerial responsibilities, the CHOs conduct screenings, manage chronic conditions, provide preventive care, and offer health education. Furthermore, the AAM initiative encourages efforts to keep all types of vacancies filled regularly at the primary level to ensure sufficient healthcare providers to meet the growing service demand. Adequate mix of offline and online training, both classroom and on the job capacity-building programs, enhance healthcare professionals' skills and knowledge, enabling them to deliver high-quality care.

Free medicines and diagnostics

Previously the selective care for Maternal and Child care enlisted limited medicines (57 at SHC) and diagnostics (7 at SHC & 19 at PHC) at primary health care facilities. Under Ayushman Bharat initiative, the list has been expanded and reorganized to 106 essential medicines at SHC, 172 essential medicines at PHC and 14 diagnostics at SHC, 63 diagnostics at PHC required for 12 packages of services at AAM.

[9] Indian Public Health Standards Guidelines 2022. National Health Mission. Accessed 27.07.2024. https://nhm.gov.in/index1.php?lang=1&level=2&sublinkid=971&lid=154

Ensuring the availability of essential medicines and diagnostic services is instrumental for the successful implementation of the AAM initiative. These drugs and diagnostics are provided free of cost resulting into significant reduction of Out-Of-Pocket Expenditure (OOPE), making healthcare more affordable and accessible to the population. This approach also enhances treatment regimen, ensures timely and appropriate patient care, reducing the need for referrals to higher-level facilities. Moreover, the country has a robust web/app based portal (Drugs & Vaccine Distribution Management System) for indent, procurement and distribution of medicines and diagnostics consumables ensuring efficient supply chain and warehousing with quality assurance features such as Prescription audit, grievance redressal etc. for monitoring the real-time status of procurement and availability of essential medicines.

Community mobilization

Community mobilization is foundational to the AAM initiative. Engaging the community ensures effective utilization of healthcare services and promotes active individual participation in health maintenance. Health promotion activities include educational campaigns, workshops, and community meetings to raise awareness about preventive measures, healthy lifestyles, and service availability at AAMs. This is bolstered through constitution of Jan Arogya Samiti, Mahila Arogya Samitis, and Village Health Sanitation and Nutrition Committee with representation from community as well as public representatives, overseeing the performance of health facilities and health workers.

Accredited Social Health Activists (ASHAs) and other community health workers play indispensable roles in mobilizing the community, conducting door-to-door visits, organizing health camps, and facilitating access to care in hard-to-reach areas. Their efforts help build trust between healthcare providers and the community, leading to improved health outcomes. Currently, there are more than one million ASHAs in-position in the country with the general norm of one ASHA per 1000 population and one ASHA per habitation in scheduled tribe areas.

Health promotion

Similar to community mobilization, health promotion and disease prevention are central to the AAM initiative with a focus on 'Illness to Wellness'. AAM facilities are equipped to conduct universal screenings for NCDs, such as diabetes and hypertension, enabling early detection and timely intervention. Additionally, AAMs promote healthy lifestyles through nutritional counselling, physical activity programs, and smoking cessation support. Wellness activities, including yoga sessions and mental health workshops, foster holistic well-being. By prioritizing preventive measures and health promotion, the initiative is resulting in reduced disease incidence and improved overall health outcomes.

Continuum of care

AAM facilities serve as the first contact point for beneficiaries, ensuring timely access to care. This approach minimizes delays in diagnosis and treatment, leading to improved and equitable health outcomes. AAM facilities are integrated into a broader healthcare network, facilitating seamless referrals to secondary and tertiary healthcare facilities when specialized care is required. With the implementation of AAM, approach to healthcare has transitioned from fragmented care to continuum of care. Robust referral systems are ensuring that the patients receive care at the appropriate level, reducing the burden on higher-level facilities and optimizing resource utilization.

Teleconsultation

Teleconsultation is expanding the reach to specialist care directly from rural and underserved areas. Integrating teleconsultation services into AAM facilities enables patients to connect with medical officers and specialists from remote locations, overcoming geographical barriers. Teleconsultation platforms such as eSanjeevani and Tele MANAS facilitate real-time communication between patients and healthcare providers, allowing accurate and timely diagnosis, treatment planning, and follow-up care. This approach enhances the reach and quality of healthcare services, reduces OOPE for patients with the need of long-distance travel in remote areas, and ensures timely consultations. Additionally, teleconsultation supports capacity building among primary care providers particularly the CHOs and Auxiliary Nurse and Midwife (ANM) at the AAM-SHC by enabling them to seek guidance from specialists for handling the patients independently in future.

Provider payment reforms

Provider payment reforms and team-based incentives are essential for the sustainability and efficiency of any health care system. The web/app based online systems to report & verify claims, followed by timely & transparent disbursal of payments & incentives in most the parts of country is helping the country to keep the health workforce motivated to deliver high-quality care. Performance-based payments are linked to specific health outcomes and quality indicators, encouraging adherence to best practices and guidelines among the primary health workforce. Moreover, these reforms align healthcare providers' financial incentives with the initiative's goals, fostering a culture of accountability and continuous improvement in healthcare delivery.

Financial support

The National Health Policy of Government of India envisions increase in public health expenditure to 2.5% of Gross Domestic Product by the year 2025 and strives to allocate two-third of total health expenditure to primary health care. National Health Mission is the one of the largest Centrally Sponsored Schemes of health supported by Government of India, with annual budget of approx. 4 Billion USD for ensuring universal access to quality health care in India. To further build a resilient health system, there is an additional central funding of 8.3 Billion USD through Finance Commission directly to local government (rural & urban) to strengthen primary healthcare system as per local needs.

To further accelerate the process, Pradhan Mantri-Ayushman Bharat Health Infrastructure Mission (PM-ABHIM) has been launched with an outlay of 7.62 billion USD to develop the capacities of primary, secondary, and tertiary care health systems, strengthen existing national institutions, and create new institutions to detect and cure new and emerging diseases.

Achievements so far

Improved access and population coverage

The AAM initiative has markedly increased access to primary healthcare services, especially in rural and underserved regions. By establishing the AAM-SHCs and AAM-PHCs, the initiative has effectively decentralized healthcare delivery, thereby reducing time to care. This decentralization approach aligns with global health strategies emphasizing the impor-

tance of accessible and equitable healthcare services. The widespread network of healthcare facilities has significantly improved population coverage. Since its implementation, the cumulative number footfall in the AAM-SHCs and AAM-PHCs have increased from 134.9 million in 2019-20 to 4.04 billion in 2024-25[10] (fig. 2).

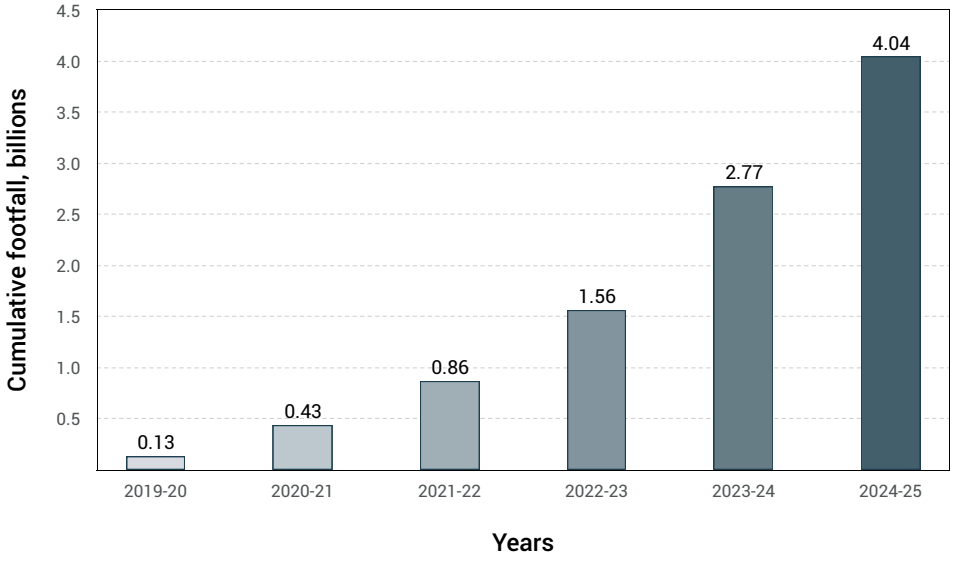
Reduced out-of-pocket expenditure

AAM has effectively reduced OOPE for individuals availing essential primary healthcare services at the AAM-SHCs and AAM-PHCs by offering services free of cost. This reduction in OOPE has facilitated improved access to essential healthcare, particularly benefiting economically disadvantaged populations. Patients referred to higher level facilities have the provision to avail services under Pradhan Mantri Jan Arogya Yojna (PM JAY) which provides a health insurance coverage of ~ 6000 USD per family per year for secondary and tertiary care hospitalization the bottom 40% of the Indian population (approx. 550 millions of beneficiaries). According to the recently published National Health Account (NHA) estimates, OOPE had accounted for 64.2% of Total Health Expenditure in 2013-14 and reduced to 39.4% in 2021-22[11].

Decongestion of secondary and tertiary healthcare facilities

The AAM initiative has contributed to the decongestion of secondary and tertiary healthcare facilities in the country by strengthening the primary healthcare infrastructure and enhancing access to essential services at the community level[12] [3]. By addressing healthcare needs at the primary level, this program has reduced the patient load on higher-level facilities, allowing them to focus on more complex and specialized treatments. This decentralization of healthcare delivery has improved the overall effi-

FIG. 2. Year wise cumulative footfall at Ayushman Arogya Mandir

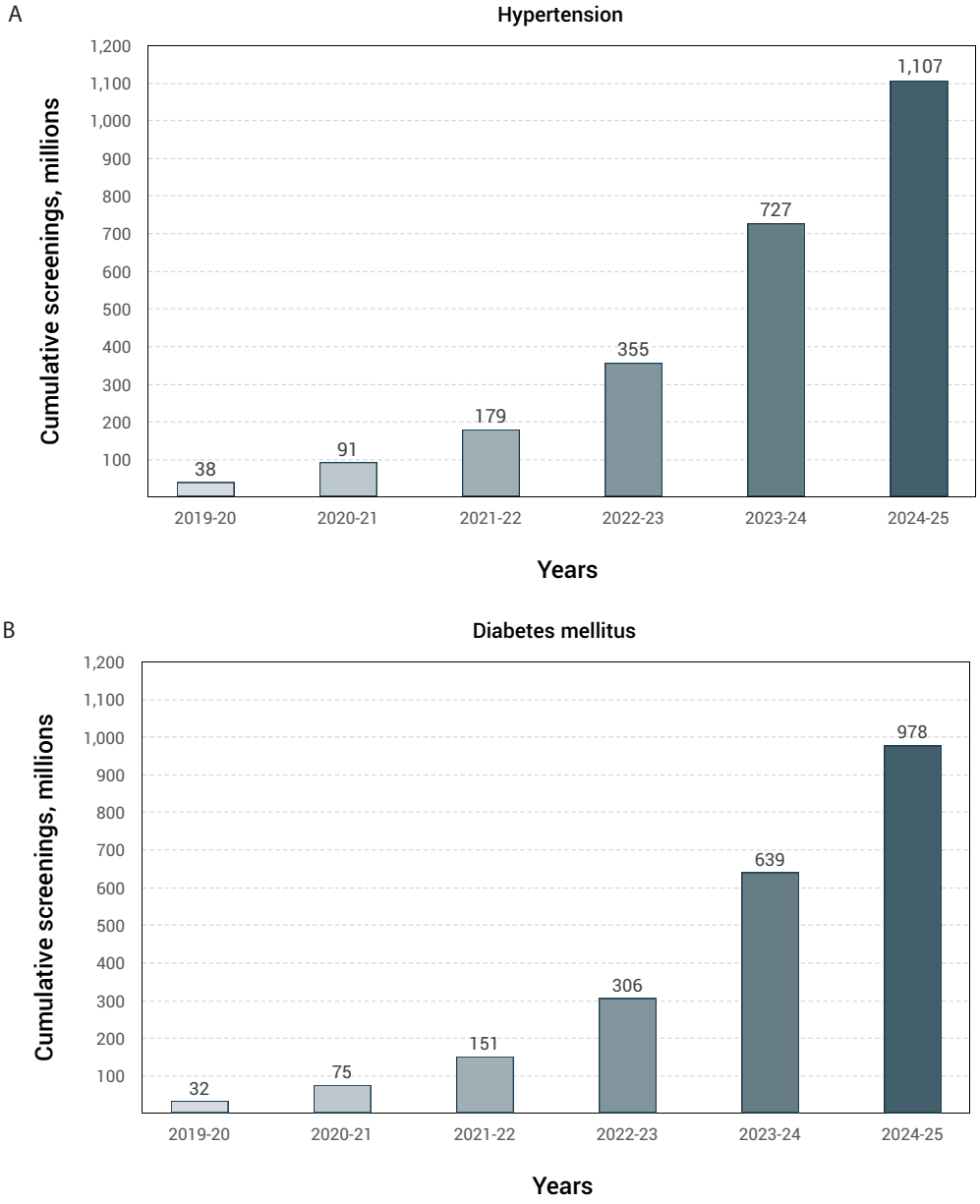


[10] Government of India, Ministry of Health and Family Welfare. Ayushman Arogya Mandir website. Updated 11.12.2019. Accessed 09.05.2025. https://ab-hwc-dev.inroad.in/

[11] National Health Accounts 2021-22. National Health Systems Resource Centre. Accessed 09.10.2024. https://nhsrcindia.org/sites/default/files/2024-09/NHA%202021-22.pdf

[12] Nirupam B, Wadhwa M. Health and Wellness Centres: Expanding Access to Comprehensive Primary Health Care in India. ICT India Working Paper #13; 2019. Accessed 27.07.2024. https://csd.columbia.edu/sites/default/files/content/docs/ICT%20India/Papers/ICT_India_Working_Paper_13.pdf

FIG. 3. Cumulative screening for hypertension and diabetes mellitus



ciency and effectiveness of the healthcare system, ensuring that secondary and tertiary institutions are not overwhelmed and can provide better quality care.

Improved population health outcomes

AAM has made a substantial impact towards improved population health outcomes in India by enhancing access to comprehensive healthcare services, particularly for economically disadvantaged groups [4]. The program's extensive coverage of essential health care services and preventive care has led to early diagnosis and timely intervention, thereby reducing morbidity and mortality rates. Maternal Mortality Rate has reduced from 122 in 2015-17 to 97 in 2018-20, Infant Mortality Rate has declined from 37 in 2015 to 28 in 2020 and Under-5 Mortality Rate has reduced

from 43 in 2015 to 32 in 2020[13]. Moreover, the financial protection offered has also alleviated economic barriers to healthcare, fostering greater utilization of health services and promoting better overall health within the population.

Improved screening for common NCDs

Historically, primary healthcare systems in India have been predominantly focused on maternal and child health services. The AAM initiative, however, adopts a more holistic approach, incorporating services for NCDs, mental health, and other specialized healthcare needs. This transition is critical in a country where NCDs account for a significant proportion of morbidity and mortality [5]. Emphasizing health promotion and disease prevention is a cornerstone of the AAM initiative. Universal screenings for NCDs such as diabetes and hypertension are conducted at the AAM-SHCs and AAM-PHCs, enabling early detection and timely intervention. From 2019-20 to 2024-25 cumulative number of screenings for hypertension increased from 38 million to more than 1.1 billion and for diabetes, increased from 32 million to 978 million (fig. 3A & 3B). Similarly, screening for three common cancers (oral, breast and cervical) has also improved[14].

Enhanced health wellness activities

Health education campaigns and wellness activities, including yoga sessions and nutritional counselling, are integral components of the AAM initiative. These measures not only foster awareness but also empower individuals to take proactive steps towards maintaining their health. As a result of the initiative, the cumulative number of wellness sessions increased from 1 million in 2019-20 to more than 52 million in 2024-25[14] (fig. 4). Evidence suggests that such integrated health promotion activities can lead to substantial improvements in community health outcomes.

Institutional reform and agent of effective implementation of all health programmes

These AAMs as against the old version of SHC have now become the example of unique experiment of institutional reform comprising all the tenets of the primary health care. As it is evident that these have become trustworthy partners in the implementation of all the health programmes of national importance, they have instilled a confidence in the policymakers to decide ambitious timelines of various health programme roll out or saturation coverage. India has launched the UWIN portal for immunisation drive to keep record of each vaccination dose, eliminate the vector borne diseases such as Kala-azar, Lymphatic Filariasis, Malaria and tuberculosis wholly realising the fact that these SHCs are now the reliable and dependable institutions for ensuring comprehensive primary health care for citizens living in rural and difficult to reach areas of country.

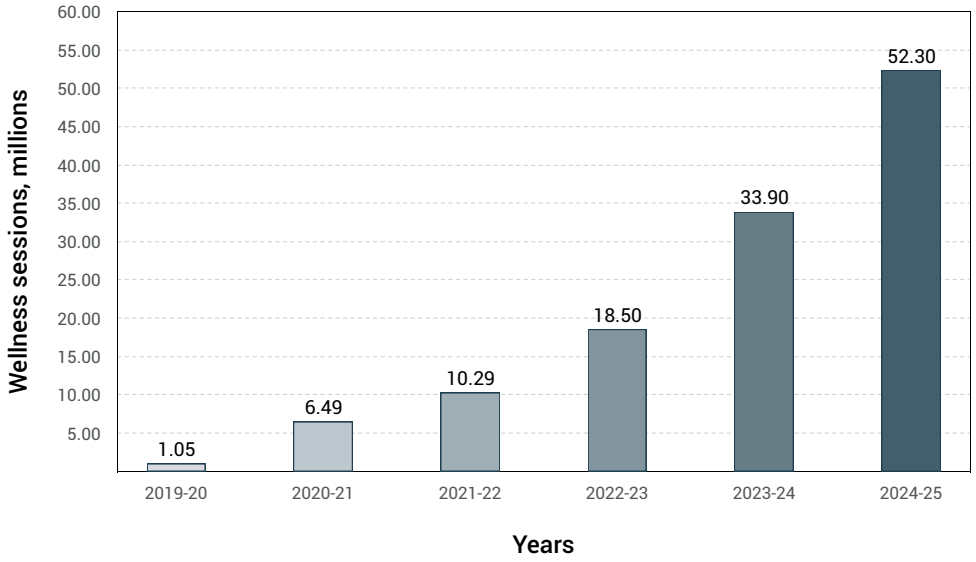
Way forward

While the progress towards citizen-friendly health care has been impressive, taking government health care services till the last mile is an area for improvement. The awareness among masses about health services, health seeking behavior and utilization of health care services in In-

[13] Office of the Registrar General & Census Commissioner, India (ORGI). Sample Registration System (SRS) – Statistical Report 2020. Census of India. Published 22.09.2022. Accessed July 27, 2024. https://censusindia.gov.in/nada/index.php/catalog/44376

[14] Government of India, Ministry of Health and Family Welfare. Ayushman Arogya Mandir website. Updated 11.12.2019. Accessed 09.05.2025. https://ab-hwc-dev.inroad.in/

FIG 4. Cumulative wellness sessions at Ayushman Arogya Mandir



dia is dynamic and dependent on multiple factors such as gender, stages of illness, literacy, socio-economic conditions, social beliefs, ease of accessibility, availability of services, time to care and quality of care etc. The efforts for provision of comprehensive care closer to the homes of people keeping along the community approach, intervened with dependable digital technologies will go a long way in reaching the unreached. The ongoing efforts for quality assurance certification (National Quality Assurance Standards issued by Ministry of Health and Family Welfare) of public health care facilities need further strengthening to enhance the trust of citizens in government health systems.

Availability of skilled healthcare workforce is critical to meet the increasing need for health care services. Innovative remuneration policies such as 'you quote we pay' for hiring the doctors to work in rural areas, skill based training, career progression through Public Health Management Cadres guidelines, residential facilities near workplace, Incentive mechanism are few sectors which will be focused in coming times.

India's ambitious initiative ABDM, is a digital ecosystem with health facility and health care provider registry, to maintain the digital health records through the unique Health ID for every individual i.e. Ayushman Bharat Health Account (ABHA ID). It will play a crucial and central role in maintaining the longitudinal electronic health records of patient enabling seamless movement of patient across the health facilities, government or private. The efforts shall have to be energised to use of this feature by maximum patients.

Additionally, impact assessments, monitoring health outcomes, and gathering feedback from beneficiaries and healthcare providers are essential to identify best practices, address challenges, and informed policy decisions.

Moreover, adequate funding on health sector as per expected norms, efficient resource utilization through inter and intra sectoral coordination will be required to sustain the initiative's gains and achieve the overall Sustainable development Goals.

Conclusion

The AAM initiative represents a paradigm shift in India's progression towards UHC, addressing systemic deficiencies within the primary healthcare infrastructure. By decentralizing service delivery and augmenting access to essential services, particularly in rural and underserved regions, the initiative has markedly improved health outcomes and reduced OOPE. Its comprehensive framework, which encompasses preventive, promotive, curative, rehabilitative, and palliative care, has alleviated the burden on secondary and tertiary care facilities, thereby enhancing the overall efficiency and efficacy of the healthcare system. Notwithstanding challenges such as infrastructural inadequacies and workforce shortages, the successful implementation of the AAM initiative has the potential to further advance healthcare equity and improve the quality of healthcare services in the country. Future initiatives must prioritize infrastructure enhancement, adequate human resource deployment, and the integration of technological innovations to consolidate and extend the progress achieved, ultimately furthering the nation’s trajectory towards UHC.

References

1. Jungo KT, Anker D, Wildisen L. Astana declaration: a new pathway for primary health care. *Int J Public Health*. 2020;65(5):511-512. doi:10.1007/s00038-020-01368-5
2. Chauhan V, Dumka N, Hannah E, et al. Mid-level health providers (MLHPs) in delivering and improving access to primary health care services – a narrative review. *Dialogues Health*. 2023;3:100146. Published 2023 Jul 4. doi:10.1016/j.dialog.2023.100146
3. Brar S, Purohit N, Singh G, et al. Health system readiness for roll out of the Ayushman Bharat Health and Wellnes Centres – Early experiences from Punjab State. *J Family Med Prim Care*. 2022;11(4):1354-1360. doi:10.4103/jfmpc.jfmpc_2560_20
4. Kamath R, Brand H. A Critical Analysis of the World's Largest Publicly Funded Health Insurance Program: India's Ayushman Bharat. *Int J Prev Med.* 2023;14:20. Published 2023 Feb 18. doi:10.4103/ijpvm.ijpvm_39_22
5. Thakur JS, Paika R, Singh S. Burden of noncommunicable diseases and implementation challenges of National NCD Programmes in India. *Med J Armed Forces India.* 2020 Jul;76(3):261-267. doi: 10.1016/j.mjafi.2020.03.002.

The BRICS HEALTH JOURNAL 2025; 2 (1): 38-52

journal homepage: https://www.bricshealthjournal.com
https://doi.org/10.47093/3034-4700.2025.2.1.38-52

ORIGINAL ARTICLE

Healthy lifestyles of contemporary Chinese population: challenges and new initiatives in primary cancer prevention

Mengyao Wu*, Huang Huang*, Peiyuan Sun, Ranran Qie, Zhuolun Hu, Qi Yan, Ruiying Fu, Yubing Lin, Xiuqi Ma, Yawei Zhang, Jie He

ORCID numbers: Mengyao Wu 0009-0004-9465-6381; Huang Huang 0000-0003-0147-9650; Peiyuan Sun 0000-0002-2134-3163; Ranran Qie 0000-0002-2801-9403; Zhuolun Hu 0000-0001-5683-1549; Qi Yan 0009-0002-8760-8889; Ruiying Fu 0000-0001-8847-3512; Yubing Lin 0009-0000-1442-9615; Xiuqi Ma 0000-0002-0768-3903; Yawei Zhang 0000-0002-9762-7752; Jie He 0000-0002-0285-5403

Correspondence to: Dr. Jie He, President, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.
Address: Beijing, 100021, China.
E-mail: hejie@cicams.ac.cn

Mengyao Wu, PhD candidate, Department of Cancer Prevention and Control, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

Huang Huang, PhD, Department of Cancer Prevention and Control, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

Peiyuan Sun, PhD candidate, Department of Cancer Prevention and Control, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

Ranran Qie, PhD, Department of Cancer Epidemiology, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Henan Engineering Research Center of Cancer Prevention and Control, Henan International Joint Laboratory of Cancer Prevention, Zhengzhou, Henan, China

Zhuolun Hu, MSPH, Department of Cancer Prevention and Control, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

Qi Yan, PhD candidate, Department of Cancer Prevention and Control, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

Ruiying Fu, PhD candidate, Department of Cancer Prevention and Control, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

Yubing Lin, Master candidate, Department of Cancer Prevention and Control, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

Xiuqi Ma, PhD, Department of Cancer Prevention and Control, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

Contributors: Yawei Zhang designed and conducted the research. Mengyao Wu performed statistical analysis. Yawei Zhang, Huang Huang, and Mengyao Wu drafted the manuscript. Huang Huang, Peiyuan Sun, Ranran Qie, Zhuolun Hu, and Yawei Zhang contributed to data collection. Mengyao Wu, Huang Huang, Peiyuan Sun, Ranran Qie, Zhuolun Hu, Qi Yan, Ruiying Fu, Yubing Lin, Xiuqi Ma, Jie He, and Yawei Zhang revised the paper critically for important content. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors read and approved the final version of the manuscript.

Informed consent statement: Not required

Funding: This study was supported by the Nonprofit Central Research Institute Fund of Chinese Academy of Medical Sciences (grant number 2021-RC310-009), the Capital's Funds for Health Improvement and Research (grant number 2022-1G-4023), and the National Natural Science Foundation of China (grant number 82204168).

Competing interests: The authors declare that they have no conflict of interest.

Ethical approval: Not required.

Data sharing: All researchers in this study group welcome potential collaboration to maximize the use of data. A data dictionary and study protocol are available upon request by contacting the research group. Upon reasonable request, the datasets generated and analyzed during the current study are available, and the research group can provide descriptive data in table form. Requests can be made to Yawei Zhang (zhangya69@foxmail.com).

Acknowledgments: The authors thank all research staff members who participated in our study.

Manuscript source: Unsolicited manuscript

Country/Territory of origin: China

Received: 20.02.2025
Accepted: 22.04.2025
Date of publication: 19.05.2025

Yawei Zhang, PhD, Chair, Department of Cancer Prevention and Control, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

Jie He, MD, President, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China

*Mengyao Wu and Huang Huang contributed equally

ABSTRACT

Background: Greater than 40% of cancer can be prevented through modifiable risk factors. The World Cancer Research Fund and American Institute for Cancer Research recommended healthy lifestyles for cancer prevention. No study, however, has investigated adoption rate of cancer prevention lifestyles in China. The aim of this study is to assess healthy lifestyle adoption among Chinese population.

Materials and methods: utilized data from a baseline survey of major cancer related risk factors in China including 89,045 participants.

Results: The results showed that the adoption rate of healthy lifestyles for cancer prevention among the contemporary Chinese population was 24.49%. Women (28.91%), individuals aged 40 years or older (26.43%-38.41%), had lower education level (27.60%), lived in rural areas (29.24%) and high or middle human development index regions (24.98%), and were unemployed (29.14%) had higher adoption rates. The adoption rate of healthy lifestyles was lowest among participants aged 25–29 years (14.16%) and showed an increased trend with age (P for trend < 0.001), with similar trends observed across subgroups stratified by sex, education level, residential area, and employment status (all P for trend < 0.001).

Conclusion: Despite challenges in implementing primary cancer prevention, recent initiatives such as China Code Against Cancer and the Smart Health Management Digital Platform for Primary Cancer Prevention are expected to promote healthy lifestyles among the Chinese population, supported by national policies and international guidelines.

Key Words: preventive oncology; modifiable risk factors; lifestyle adoption; Smart Health Management; Code Against Cancer

Citation: Wu M, Huang H, Sun P, Qie R, Hu Z, Yan Q, Fu R, Lin Y, Ma X, Zhang Y, He J. Healthy lifestyles of contemporary Chinese population: challenges and new initiatives in primary cancer prevention. *The BRICS Health Journal.* 2025;2(1):38-52. https://doi.org/10.47093/3034-4700. 2025.2.1.38-52

Introduction

Non-communicable diseases (NCDs), including cancer, become a significant public health challenge, hindering progress toward the Sustainable Development Goals. NCDs accounted for 75% of non-pandemic-related deaths worldwide in 2021, with the majority occurring in low- and middle-income countries[1]. Cancer is responsible for about 10 million deaths annually, second only to cardiovascular disease as the leading cause of NCD death globally[2] [1]. In China, there are 4.8 million new cases and 2.6 million deaths each year, accounting for approximately one-fourth of global cancer incidence and mortality respectively [2]. The cancer burden in China is expected to grow by about 50% in the next two decades,

[1] World Health Organization. Non communicable diseases. Accessed March 14, 2025. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases
[2] International Agency for Research on Cancer. Global Cancer Observatory. Accessed 16.02.2025. https://gco.iarc.fr/ Office of the Leading Group of the State

driven by the rapidly growing aging population, industrialization, and widespread unhealthy lifestyles [3]. Growing evidence indicates that more than 40% of cancers are preventable by addressing modifiable risk factors [4]. Recommendations from the World Health Organization suggest that reducing unhealthy behaviors is one of the most cost-effective ways to tackle NCDs including cancer [5, 6]. Aligning with the "Healthy China 2030" strategy, promoting healthy lifestyles and early intervention is crucial for reducing the cancer burden in China and worldwide.

Lifestyle risk factors, including unhealthy diet, alcohol consumption, physical inactivity, obesity, and tobacco use, contributed to more than 40% of global cancer deaths and disability-adjusted life-years [7], and China shared the same situation [8]. These individual lifestyle factors often co-exist and have synergistic effect on health [9]. World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) made recommendations on healthy lifestyles for cancer prevention, including being a healthy weight, being physically active, eating a diet rich in wholegrains, vegetables, fruits, and beans, limiting consumption of fast food and other processed foods, limiting consumption of red and processed meat, limiting consumption of sugar-sweetened drinks, and limiting alcohol consumption [10]. Multiple studies have provided supporting evidence that individuals who adhere to the 2018 WCRF/AICR recommendations experienced a reduced risk of breast, colorectal, and lung cancer, highlighting that promoting healthy lifestyles can serve as a primary cancer prevention strategy [11, 12].

Several studies from North America, Europe, and Africa reported on the prevalence of adherence to the 2018 WCRF/AICR recommendations and found wide variation between study populations, ranging from 6.28% to 40.1%, suggesting that there is considerable scope for promoting healthy lifestyles [11, 13–27]. No study has investigated compliance with the 2018 WCRF/AICR recommendations among Chinese populations.

This study analyzed data from an ongoing population-based study of major cancer related risk factors in China to understand the status of healthy lifestyles of the contemporary Chinese population follows the 2018 WCRF/AICR recommendations, identify challenges in promoting healthy lifestyles, and share new initiatives in promoting healthy lifestyles.

Materials and methods

All data was from a baseline survey of major cancer-related risk factors in China between 07.07.2021 and 31.12.2024, including 148,338 participants. All participants were enrolled through the Smart Health Management Digital Platform for Primary Cancer Prevention (SmartHMDP-PCP) with an electronic module-based standardized questionnaire including information on demographic characteristics, lifestyle and environmental factors, medical history and medication use, and family history [28]. Majority of the study participants were from Beijing, Guangdong, Shaanxi, Henan, Gansu, Shanxi, and Sichuan provinces in China. Participants with missing data on variables in the 2018 WCRF/AICR recommendations (N=59,293) were excluded, yielding 89,045 participants being included for the final analysis. Electronic informed consents were obtained from all participants before investigation. This study was approved by the ethical committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences.

The 2018 WCRF/AICR score was calculated by assigning the points of 1, 0.5, and 0 to fully, partially, and not meeting each of the recommended items, respectively. The 2018 WCRF/AICR score is represented in Supple-

ment A (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.38-52-annex-a). Physical activity was calculated as minutes per week through frequency and duration of moderate-vigorous leisure-time physical activity (e.g., yoga, walking, running, cycling, swimming), transport physical activity (e.g., walking briskly, running), household physical activity (e.g., child care, family care, yard work, scrubbing floors), and occupational physical activity. Total duration of moderate-vigorous physical activity was categorized into ≥150, 75-<150 and <75 mins/week. Dietary information was collected via a semi-quantitative food frequency questionnaire. The intake of fruits and vegetables was divided into three classes: ≥400, 200-<400, and <200 g/day. Total fiber intake was estimated from the frequency of consumption and portion size of food items using the Chinese standard tables of food consumption and subsequently categorized into ≥30, 15-<30, and <15 g/day [29, 30]. Alcohol consumption was based on daily ethanol intake of beer, grape wine, rice wine, and liquor. Sex-specific classification of daily ethanol intake was used in scoring alcohol consumption: fully (0 g/day), partially (>0-28 g/day for males and >0-14 g/day for females), and not meeting the recommendation (>28 g/day for males and >14 g/day for females). Red meat intake was categorized as <300, 300-500, and >500 g/week. Total sugar-sweetened drinks intake was categorized into <1, 1-2, and ≥3 can/day. The cutoffs of body mass index (BMI; underweight: <18.5, healthy weight: 18.5-<24, overweight: 24-<28, and obesity: ≥28.0 kg/m^2) were based on the criteria proposed by the Working Group on Obesity in China [31]. We used takeaways to replace fast food and was categorized into <1, 1-3, and ≥4 time/week. The final score was the sum of all points of seven items, with higher values indicating healthier lifestyle. The score was further categorized into unhealthy (0-4 points), moderately healthy (>4-<6 points), and healthy (6-7 points).

Characteristics of the study population were presented as numbers (percentages) for qualitative variables, and median (interquartile range) for quantitative variables, by the 2018 WCRF/AICR Score groups. Chi-square tests or Kruskal-Wallis tests were used to compare differences among the 2018 WCRF/AICR Score groups. The weights of the Segi's population and China's 2020 Census for calculating age-standardized prevalence rates (ASPR) of three lifestyle groups, respectively[3,4]. The linear trends of prevalence over age groups were tested using Cochran-Armitage test, both overall and by certain selected subgroups of individuals (e.g., sex, education, urban-rural location, employment status, geographic region, and regional human development index (HDI)). According to Human Development Report Office, regional HDI was divided into low (<0.550), medium (0.550-0.699), high (0.700-0.799), and very high (≥0.800)[5]. All statistical analyses were done with SAS version 9.4 and R version 4.3.2. Two-sided P value <0.05 was considered as statistical significance.

Results

Among 89,045 participants, the median (interquartile range) age was 38 (29-48) years and 57,384 (64.44%) were women. Of the overall population, 21,803 (24.49%) adopted healthy lifestyles, 54,279 (60.96%) adopted

[3] Office of the Leading Group of the State Council for the Seventh National Population Census. China Population Census Yearbook 2020. Beijing: China Statistic Press. 2022

[4] Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJ, Lozano R, Inoue M. Age standardization of rates: a new WHO standard. Geneva: World Health Organization; 2001. Accessed 16.02.2025. https://cdn.who.int/media/docs/default-source/gho-documents/global-health-estimates/gpe_discussion_paper_series_paper31_2001_age_standardization_rates.pdf

[5] United Nations Development Programme. Human Development Index (HDI). United Nations Development Programme. Accessed 16.02.2025. https://hdr.undp.org/data-center/human-development-index#/indicies/HDI

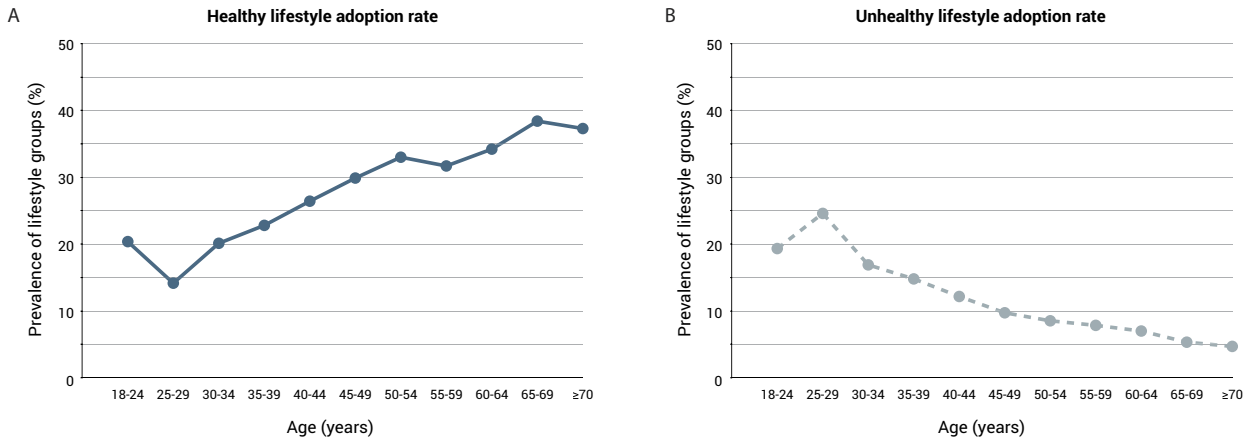
Table. Characteristics of participants by the 2018 WCRF/AICR Lifestyle.

Characteristic	The 2018 WCRF/AICR Lifestyle										P-value
	Overall		Healthy (6-7 points)				Unhealthy (0-4 points)				
	N	Percent	N	Crude rate	ASPR (World)	ASPR (China)	N	Crude rate	ASPR (World)	ASPR (China)	
Overall	89,045		21,803	24.49%	26.08%	27.83%	12,963	14.56%	13.50%	12.01%	
Sex											
Women	57,384	64.44%	16,587	28.91%	31.39%	33.59%	6,330	11.03%	9.95%	8.53%	<0.001
Men	31,661	35.56%	5,216	16.47%	17.68%	19.25%	6,633	20.95%	20.26%	18.31%	
Education											
Below bachelor's degree	40,397	45.37%	11,150	27.60%	26.64%	28.40%	5,179	12.82%	13.89%	12.23%	
Bachelor's degree and above	48,556	54.53%	10,640	21.91%	25.88%	27.84%	7,770	16.00%	13.54%	12.19%	<0.001
Missing	92	0.10%	13				14				
Urban-rural location											
Rural	23,272	26.14%	6,805	29.24%	29.45%	30.81%	2,510	10.79%	10.59%	9.42%	
Urban	64,762	72.73%	14,756	22.78%	24.98%	26.85%	10,306	15.91%	14.50%	12.92%	<0.001
Missing	1,011	1.14%	242				147				
Employment status											
Unemployed	28,331	31.82%	8,257	29.14%	29.76%	31.26%	3,170	11.19%	10.71%	9.54%	<0.001
Employed	60,714	68.18%	13,546	22.31%	24.25%	26.38%	9,793	16.13%	15.68%	13.95%	
Geographic region											
South	14,858	16.69%	2,308	15.53%	18.29%	20.53%	3,175	21.37%	19.90%	17.86%	
North	74,178	83.30%	19,492	26.28%	27.65%	29.29%	9,787	13.19%	12.23%	10.85%	<0.001
Missing	9	0.01%	3				1				
Regional HDI											
Very high	10,839	12.17%	2,267	20.92%	20.94%	23.21%	1,872	17.27%	18.36%	15.89%	
Middle-to-high	78,203	87.82%	19,535	24.98%	26.86%	28.63%	11,091	14.18%	13.03%	11.61%	<0.001
Missing	3	0.00%	1				0				
Age group (years)											
18-24	13,384	15.03%	2,727	20.38%			2,589	19.34%			
25-29	9,982	11.21%	1,413	14.16%			2,456	24.60%			
30-34	13,570	15.24%	2,731	20.13%			2,293	16.90%			
35-39	12,812	14.39%	2,922	22.81%			1,896	14.80%			
40-44	11,146	12.52%	2,946	26.43%			1,357	12.17%			
45-49	9,751	10.95%	2,915	29.89%			949	9.73%			<0.001
50-54	9,013	10.12%	2,975	33.01%			769	8.53%			
55-59	4,953	5.56%	1,570	31.70%			389	7.85%			
60-64	2,101	2.36%	719	34.22%			147	7.00%			
65-69	1,333	1.50%	512	38.41%			71	5.33%			
≥70	1,000	1.12%	373	37.30%			47	4.70%			

Note: WCRF/AICR – World Cancer Research Fund/ American Institute for Cancer Research, ASRP – age-standartized prevalence rate, HDI – human development index.

moderately healthy lifestyles, and 12,963 (14.56%) adopted unhealthy lifestyles. The ASPR using the world standard population of healthy, moderately healthy, and unhealthy lifestyle were 26.08%, 60.42%, and 13.50%, respectively. The ASPR (world) of a healthy lifestyle was higher among women, individuals with education below a bachelor's degree,

FIG. 1. Age-specific adoption rates of healthy and unhealthy lifestyle in 2018 WCRF/AICR groups.



Note: All P for trends were <0.001. WCRF/AICR – World Cancer Research Fund/ American Institute for Cancer Research.

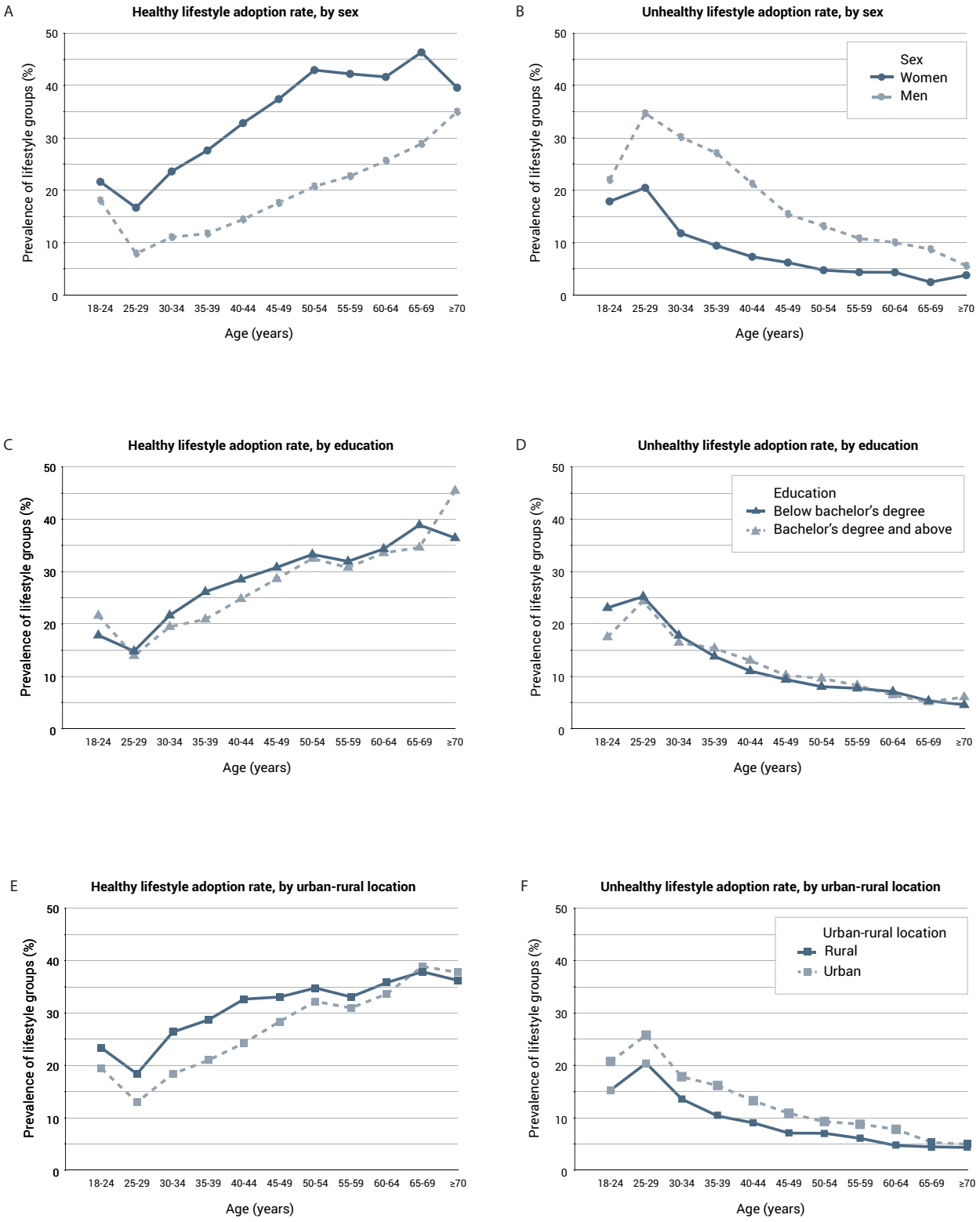
those who were unemployed, and those residing in rural locations, northern regions, and regions with middle-to-high HDI (all P<0.001; Table).

The adoption rate of healthy lifestyles was lowest among participants aged 25–29 years (14.16%) and increased with age (P for trend < 0.001), peaking at the 65–69-year age group (38.41%), except for a slight decline observed in those aged 55–59 years (31.70%) (Fig. 1). Conversely, the adoption rate of unhealthy lifestyles followed the opposite pattern, showing a decreasing trend with age (P for trend < 0.001), with the highest level in the 25–29-year age group (24.60%) and declining to the lowest among those aged 70 years or older (4.70%). The similar lifestyle patterns were observed in subgroups stratified by sex, educational level, residential areas, and employment status (all P for trend < 0.001, Fig. 2). However, men consistently had lower adoption rates of healthy lifestyles and higher adoption rates of unhealthy lifestyles across all age groups as compared to women.

The age-specific adoption rates of healthy lifestyles were slightly higher among participants without a bachelor's degree than those with a bachelor's degree or above across the 25–29 to 65–69-year age groups. Compared with rural residents, urban participants had lower adoption rates of healthy lifestyles across all age groups except those aged 65 years or older, while the adoption rate of unhealthy lifestyles was higher among urban residents across all age groups. Among unemployed participants, the trend of healthy lifestyles almost mirrored that of the overall population, whereas among employed individuals, adoption rate increased from the 18-24-year (12.68%) to 50-54-year (32.01%) age groups before fluctuating in those aged 55 years or older, although the overall trend remained increasing. The adoption rate of unhealthy lifestyles was consistently higher among employed participants than unemployed individuals across all age groups.

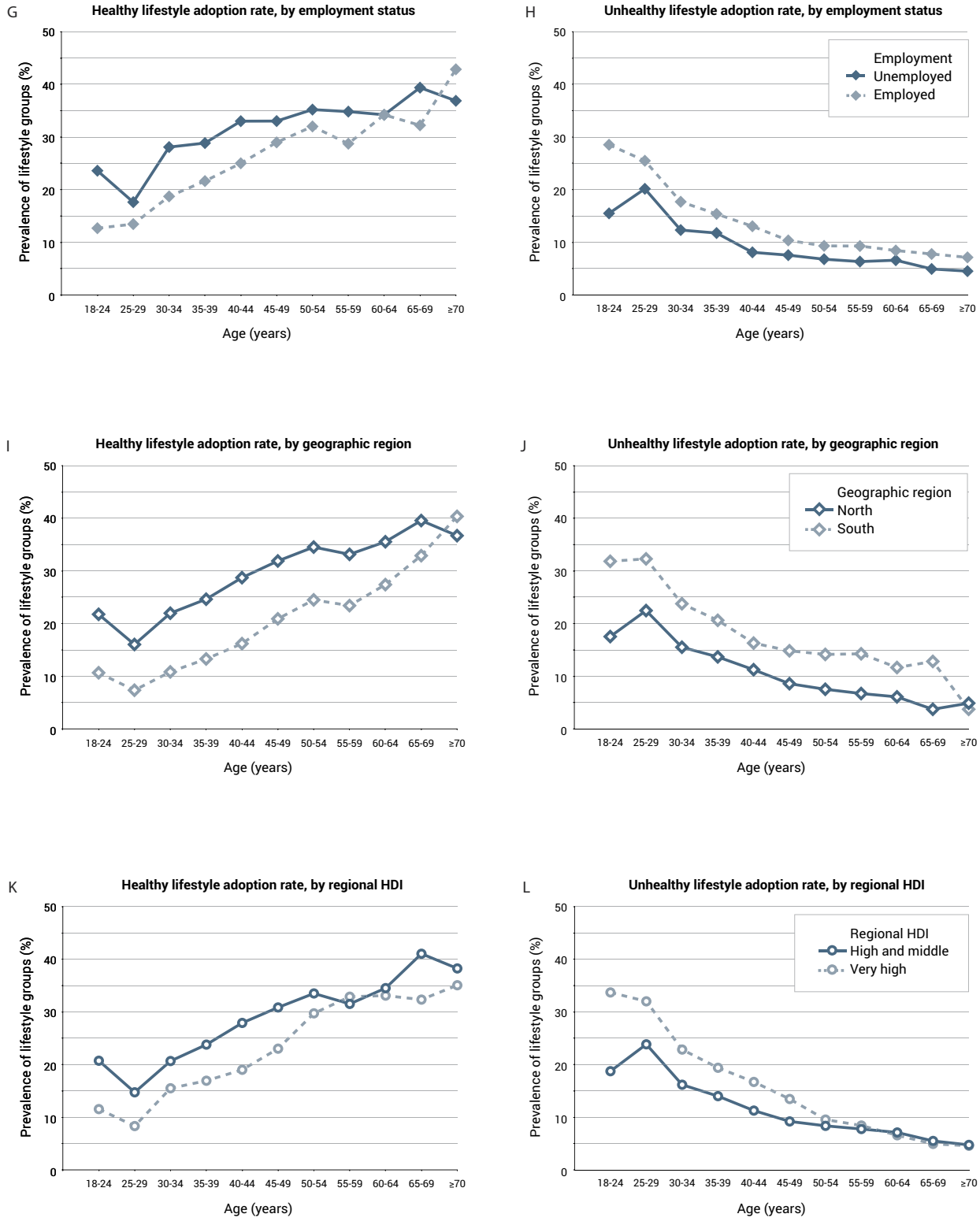
Regional disparities were also observed. In northern China, the adoption rate of healthy lifestyles was higher, and that of unhealthy lifestyles was lower across all age groups except in the age group of 70 years or older. Stratification by regional HDI showed that participants living in very high HDI regions generally had lower adoption rates of healthy lifestyles, except in the 55–59-year age group. On the other hand, the adoption rate

FIG. 2. Age-specific adoption rates of healthy and unhealthy lifestyle in 2018 WCRF/AICR groups, among subgroups.



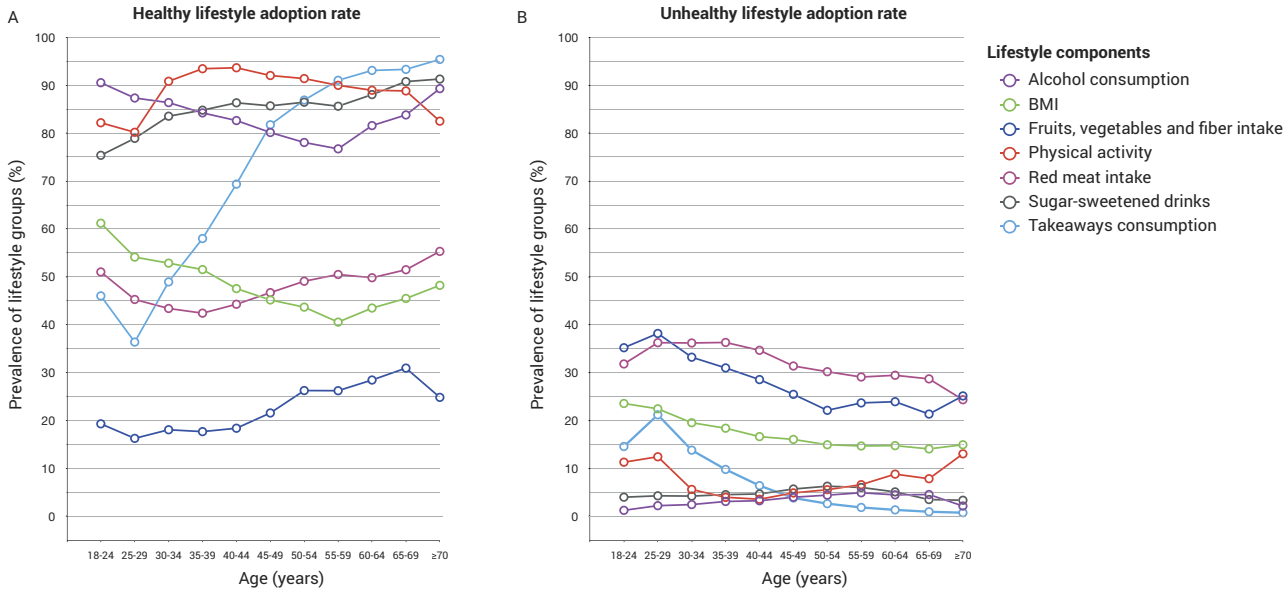
Note: All P for trend were <0.001 in all groups. WCRF/AICR – World Cancer Research Fund/ American Institute for Cancer Research, HDI – Human Development Index.

FIG. 2. (Continued). Age-specific adoption rates of healthy and unhealthy lifestyle in 2018 WCRF/AICR groups, among subgroups.



Note: All P for trend were <0.001 in all groups. WCRF/AICR – World Cancer Research Fund/ American Institute for Cancer Research, HDI – Human Development Index.

FIG. 3. Age-specific adoption rates of healthy (A) and unhealthy (B) lifestyle in 2018 WCRF/AICR components.



Note: For single lifestyles, healthy lifestyle represented "1 point" for the correspondent recommendation, and unhealthy lifestyle represented "0 points". All P for trend were <0.001 in all groups. WCRF/AICR – World Cancer Research Fund/ American Institute for Cancer Research, BMI – body mass index.

of unhealthy lifestyles was higher in very high HDI regions for all age groups before 60–64 years.

We further analyzed single lifestyle components, and found that adherence to recommendations regarding fruit, vegetable, and fiber intake was the lowest across all age groups (all age-specific prevalences <40%; Fig. 3). Similarly, adherence to BMI recommendations and red meat intake guidelines was relatively low. In contrast, adherence to physical activity, sugar-sweetened drinks intake, and alcohol consumption guidelines was relatively higher. Older participants demonstrated greater adherence to recommendations for takeaway food consumption, sugar-sweetened drinks intake, red meat intake, and fruit, vegetable, and fiber intake. Among them, adherence to recommendations on takeaway food consumption showed substantial changes with age, with a marked increase starting from the 25–29 years (36.35%) to 70 years or older (95.40%) age group. Conversely, the age-specific adoption rate of unhealthy adherence followed the opposite trend.

Discussion

Status of healthy lifestyles of contemporary Chinese population

To the best of our knowledge, this represents the first study to report the prevalence of combined lifestyles in adherence to the 2018 WCRF/AICR recommendations in a Chinese population. This study found that approximately a quarter of the people had healthy lifestyles. In general, women, older individuals, people lived in rural areas, and people lived in middle-to-high HDI regions were more likely to adopt healthy lifestyles. While compliance with the 2018 WCRF/AICR recommendations in this study was comparable to other studies, the fact that only about one fourth

of the overall population and less than one fifth of young people adopted healthy lifestyles suggests that more efforts are needed to increasing adoption rates.

According to a national health literacy monitoring survey in 2021 in China, individuals with higher educational levels possessed greater health literacy than those with lower educational levels [32]. However, our study did not observe a higher prevalence of healthy lifestyles among people with greater education levels. In developing counties like China, development of health-supportive system might lag behind rapid social and economic transformations, causing the health penalty to high social economic status individuals [33]. On the other hand, unhealthy dietary and drinking options were less affordable and often perceived as privileges of the advantaged individuals. Other potential explanations may be due to lack of effective health education regarding primary cancer prevention. More efforts are needed to explore potential barriers to people adopting healthy lifestyles. Notably, the government launched the "Weight Management Year" initiative, aiming to promote healthy lifestyles, with a particular focus on a healthy lifestyle friendly environment[6].

In China, 920 million people lived in urban areas and 733 million were employed[7]. These employed and lived in very high HDI regions and in urban areas often have greater financial power to afford unhealthy behaviors. Meanwhile, the fast-paced life, high work demand, extended working hours, job insecurity, and commuting difficulties made it difficult for people to adopt a healthy lifestyle [34]. In our study men had significant lower rate of adopting healthy lifestyles compared to women, indicating that sex imbalance in social role might adversely affect men's engagement in healthy lifestyles in China. Therefore, in addition to promoting health literacy, building a more supportive working and living environment is also essential in facilitating healthy lifestyle, such as creating healthy canteens, corporate gyms, and discouraging alcohol-based socializing.

All study participants were smartphone users who completed online surveys, the findings may not be generalizable to non-smartphone users in China, especially older adults. We reported age-standardized rates to address the concerns that majority of our study population were under 60 years old. In this study, takeaways, which included healthy and unhealthy options, were used to replace ultra-processed food, might introducing potential misclassification. Although the relationship between 2018 WCRF/AICR recommendations and cancer risk among Chinese population remains to be explored, targeted strategies should be implemented to increase the rate of healthy lifestyle in adherence to the 2018 WCRF/AICR recommendations to reduce the cancer burden in China, which accounted for about one fourth of the world's newly diagnosed cancer cases in 2022 [2].

Challenges in primary cancer prevention in China

The observed low prevalence of healthy lifestyles related to cancer prevention among the Chinese population suggests existing challenges in primary cancer prevention. Lack of health knowledge and awareness, as well as health misinformation and disinformation are the most significant barriers to making informed healthy lifestyle choices. Despite increasing access to information, health education and health literacy re-

[6] The National Health Commission of the People's Republic of China. Notice on the Implementation Plan for the "Weight Management Year" Activity. (in Chinese). Accessed 16.02.2025. http://www.nhc.gov.cn/ylyjs/pqt/202406/b4f7141179504bd69d7a18db6d877f47.shtml

[7] Chinese National Bureau of Statistics. China Statistical Yearbook 2023. Beijing: China Statistics Press; 2023. Accessed 16.02.2025. https://www.stats.gov.cn/sj/ndsj/2023/indexeh.htm

main limited in many communities, making it difficult for these populations to make informed decisions about their health. On the other hand, rising social media usage, combined with anxiety and fear of cancer among the general population, has fueled the spread of a range of misleading claims about cancer prevention, which can probably lead people to disregard evidence-based preventive behaviors in favor of lifestyles endorsed by influencers, downplay the importance of mental health issues, and promote unregulated supplements [35]. Therefore, there is an urgent need to establish an authoritative evidence-based information dissemination platform for cancer risk factors and preventive intervention measures to convey the facts in a way that leaves no room for misunderstanding and to enhance the correct understanding of healthy lifestyles for cancer prevention among the Chinese population. Since barriers to adopting a healthy lifestyle may vary depending on personal characteristics, sociocultural background, and environmental factors, the dissemination of healthy lifestyle information should also be tailored to each individual [36].

Lack of motivation is another major challenge to adopting and sticking to healthy lifestyles. Many people feel overwhelmed by the thought of starting healthy behaviors, especially those who have failed in past attempts to change and stick with such behaviors. This frustration can lead to procrastination and avoidance, making it more difficult to take the first step toward a healthier lifestyle. In addition, motivation may wane over time, particularly if the immediate effects on health are not evident. Therefore, when promoting healthy lifestyles to the general population, appropriate theoretical models should be applied to attract those unmotivated people who are difficult to reach with traditional health promotion activities, cultivate their motivation for action, and increase their acceptance and persistence of healthy behaviors [37].

The Chinese population is diverse in terms of ethnicity, cultural background, geographic region, and socioeconomic status. These diversities are not only related to whether individuals actively choose a healthy lifestyle, but also to the objective accessibility of a healthy lifestyle. Mobile technology plays an increasingly important role in promoting healthy lifestyles as its low cost and multifunctionality make health resources more affordable and distributed more equitably. Mobile health (mHealth) provides easy access to information on diet and nutrition, guidance and assistance for training and exercise, and tracking and monitoring physical activity, food consumption, sleep, and phycological measurements (e.g., heart rate, blood pressure, and blood sugar), so wider use of mHealth should be encouraged to assist health promotion efforts [36].

New initiatives in primary cancer prevention in China

In 2016, China released the “Healthy China 2030” national strategic plan, which identified national health as a development priority and reflected China’s commitment to participating in global Health governance and implementing the United Nations 2030 Agenda for Sustainable Development[8] [38]. Under the framework of the “Healthy China Action Plan 2019-2030”, the State Council of China issued two versions of the Healthy China Action – Cancer Prevention and Control Implementation Plan in 2019 and 2023, respectively. These national strategies emphasized reducing exposure to cancer risk factors to prevent cancer. In line with the national policies and promoting healthy lifestyles for primary can-

[8] United Nations. Transforming our world: the 2030 Agenda for Sustainable Development. Accessed 17.02.2025. https://sdgs.un.org/2030agenda

cer prevention, the National Cancer Center of China (NCC China) developed China Code Against Cancer (CCAC) and the SmartHMDP-PCP.

China Code Against Cancer

To inform the general public about evidence-based behaviors that can be taken to reduce cancer risk, NCC China published the CCAC 2025 version and established the CCAC official website (https://ccacdcpc.org.cn/) as an authoritative communication platform for cancer-related health information. The CCAC was drafted under the general framework of the World Code Against Cancer Framework proposed by the International Agency for Research on Cancer, which was aimed to encourage countries and regions to develop regional codes against cancer according to their local characteristics [39].

The CCAC 2025 version includes 15 action-based recommendations to guide the public to adopt healthy lifestyles, avoid or reduce exposure to carcinogenic agents, and participate in vaccinations, aiming to reduce an individual's risk of developing or dying from cancer. The CCAC is presented in Supplement B (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.38-52-annex-b). All the recommendations were developed in accordance with the following principles: 1) based on strong scientific evidence, balancing risks and benefits, and posing no additional risks to individuals when implemented; 2) broadly applicable to the general Chinese population without requiring any prerequisites or expertise; 3) taking into account the spectrum of cancer burden in China, the cultural practices of different populations, and the distribution of healthcare services; and 4) able to be clearly and concisely communicated in simple, instructive language that is easy for the public to understand and follow.

Smart Health Management Digital Platform for Primary Cancer Prevention

The NCC China has also developed a smartphone health applet, the SmartHMDP-PCP, to address the challenge of lacking an effective mechanism to attract people to actively adopt and adhere to a healthy lifestyle. The SmartHMDP-PCP can serve as an innovative solution to provide a cost-effective approach for personalized cancer prevention interventions and offer sustainable incentives for the public to engage in healthy lifestyles.

The SmartHMDP-PCP is powered by mobile technology, data science, and personalized intervention strategies. It runs in the WeChat environment. People can use the applet to 1) assess their risk of developing 19 types of cancer, including the cancers of the brain, head and neck, thyroid, lung, esophagus, stomach, liver, pancreas, colorectum, kidney, bladder, female breast, ovaries, endometrium, cervix, and prostate, as well as leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma; 2) track and archive their long-term exposure to behavioral, environmental, social, psychological, medical, and metabolic factors; and 3) obtain personalized intervention strategies for healthy lifestyles to reduce their cancer risk.

The SmartHMDP-PCP has multiple advantages in healthy lifestyle assistance and primary cancer prevention. This applet is based on smart mobile devices and commonly used social software, so it can be easily accessed and used in daily life. Given the continued development of mobile technology and the increasing number of mobile technology users, the impact of such mHealth interventions is likely to expand further. In addition, the highly cost-effective nature of mHealth interventions enables them to be widely disseminated to different socioeconomic groups with-

out geographical restrictions, which can to some extent reduce potential inequalities in the distribution and access to health resources among large and diverse populations. Real-time assessment and early warning of future cancer risks, as well as interactive systems for reporting cancer-related exposures and targeted preventive interventions, can potentially improve user engagement and compliance. The personalized health education and cancer prevention interventions provided by SmartHMDP-PCP achieved two-stage behavior changes by promoting health cognition and reducing action barriers, respectively. There is evidence that health interventions based on both cognitive and proactive phases of behavior change are more effective than interventions based on either phase alone [40]. In addition, personalized health information and intervention strategies are more likely to increase individual engagement and trigger central persuasion pathways, leading to a stable motivational effect during application [40]. The SmartHMDP-PCP also used the health belief model and protection motivation theory to further enhance the effect of behavior change. The cancer risk early warning system can serve as a threat trigger to motivate individuals to take actions to promote health and prevent cancer. The engagement and retention of SmartHMDP-PCP users are also key factors in achieving a long-term and sustainable healthy lifestyle, as significant health effects require a certain level intensity and persistence of intervention.

In conclusion, there are variations of healthy lifestyles adoption rates among the contemporary Chinese population. CCAC provides an authoritative platform for disseminating evidence-based information, and SmartHMDP-PCP provides novel approaches for individualized primary cancer prevention, putting national policies into practice. Further implementation and continuous evaluation and updating are necessary to achieve optimistic adoption rates of healthy lifestyles.

References:

1. GBD 2013 DALYs and HALE Collaborators, Murray CJL, Barber RM, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. *Lancet.* 2015;386(10009):2145-2191. doi:10.1016/S0140-6736(15)61340-X
2. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians.* 2024;74(3):229-263. doi:10.3322/caac.21834
3. Brennan P, Davey-Smith G. Identifying Novel Causes of Cancers to Enhance Cancer Prevention: New Strategies Are Needed. *J Natl Cancer Inst.* 2022;114(3):353-360. doi:10.1093/jnci/djab204
4. World Health Organization. *Cancer Control: Knowledge into Action: WHO Guide for Effective Programmes: Module 2: Prevention [M]. Geneva: World Health Organization*; 2007. 56 p; ISBN 92 4 154711 1
5. Bray F, Jemal A, Torre LA, Forman D, Vineis P. Long-term Realism and Cost-effectiveness: Primary Prevention in Combatting Cancer and Associated Inequalities Worldwide. *J Natl Cancer Inst.* 2015;107(12):djv273. doi:10.1093/jnci/djv273
6. Khushalani JS, Song S, Calhoun BH, Puddy RW, Kucik JE. Preventing Leading Causes of Death: Systematic Review of Cost-Utility Literature. *Am J Prev Med*. 2022;62(2):275-284. doi:10.1016/j.amepre.2021.07.019
7. GBD 2019 Cancer Risk Factors Collaborators. The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* 2022;400(10352):563-591. doi:10.1016/S0140-6736(22)01438-6
8. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its

provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2019;394(10204):1145-1158. doi:10.1016/S0140-6736(19)30427-1
9. McAloney K, Graham H, Law C, Platt L. A scoping review of statistical approaches to the analysis of multiple health-related behaviours. *Preventive Medicine.* 2013;56(6):365-371. doi:10.1016/j.ypmed.2013.03.002
10. Shams-White MM, Brockton NT, Mitrou P, et al. Operationalizing the 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Cancer Prevention Recommendations: A Standardized Scoring System. *Nutrients.* 2019;11(7):1572. doi:10.3390/nu11071572
11. Shams-White MM, Brockton NT, Mitrou P, Kahle LL, Reedy J. The 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Score and All-Cause, Cancer, and Cardiovascular Disease Mortality Risk: A Longitudinal Analysis in the NIH-AARP Diet and Health Study. *Curr Dev Nutr.* 2022;6(6):nzac096. doi:10.1093/cdn/nzac096
12. Malcomson FC, Wiggins C, Parra-Soto S, et al. Adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research Cancer Prevention Recommendations and cancer risk: A systematic review and meta-analysis. *Cancer.* 2023;129(17):2655-2670. doi:10.1002/cncr.34842
13. Onyeaghala G, Lintelmann AK, Joshu CE, et al. Adherence to the World Cancer Research Fund/American Institute for Cancer Research cancer prevention guidelines and colorectal cancer incidence among African Americans and whites: The Atherosclerosis Risk in Communities study. *Cancer.* 2020;126(5):1041-1050. doi:10.1002/cncr.32616
14. Zhang ZQ, Li QJ, Hao FB, et al. Adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research cancer prevention recommendations and pancreatic cancer incidence and mortality: A prospective cohort study. *Cancer Med.* 2020;9(18):6843-6853. doi:10.1002/cam4.3348
15. Kaluza J, Harris HR, Håkansson N, Wolk A. Adherence to the WCRF/AICR 2018 recommendations for cancer prevention and risk of cancer: prospective cohort studies of men and women. *Br J Cancer*. 2020;122(10):1562-1570. doi:10.1038/s41416-020-0806-x
16. Barrubés L, Babio N, Hernández-Alonso P, et al. Association between the 2018 WCRF/AICR and the Low-Risk Lifestyle Scores with Colorectal Cancer Risk in the Predimed Study. *J Clin Med.* 2020;9(4):1215. doi:10.3390/jcm9041215
17. Arthur RS, Wang T, Xue X, Kamensky V, Rohan TE. Genetic Factors, Adherence to Healthy Lifestyle Behavior, and Risk of Invasive Breast Cancer Among Women in the UK Biobank. J Natl Cancer Inst. 2020;112(9):893-901. doi:10.1093/jnci/djz241
18. Barrios-Rodríguez R, Toledo E, Martinez-Gonzalez MA, et al. Adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research Recommendations and Breast Cancer in the SUN Project. *Nutrients.* 2020;12(7):2076. doi:10.3390/nu12072076
19. Hermans KEPE, van den Brandt PA, Loef C, Jansen RLH, Schouten LJ. Adherence to the World Cancer Research Fund and the American Institute for Cancer Research lifestyle recommendations for cancer prevention and Cancer of Unknown Primary risk. *Clin Nutr.* 2022;41(2):526-535. doi:10.1016/j.clnu.2021.12.038
20. Karavasiloglou N, Pestoni G, Kühn T, Rohrmann S. Adherence to cancer prevention recommendations and risk of breast cancer in situ in the United Kingdom Biobank. *Int J Cancer.* 2022;151(10):1674-1683. doi:10.1002/ijc.34183
21. Malcomson FC, Parra-Soto S, Lu L, et al. Socio-demographic variation in adherence to the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) Cancer Prevention Recommendations within the UK Biobank prospective cohort study. *J Public Health (Oxf).* Published online November 20, 2023:fdad218. doi:10.1093/pubmed/fdad218
22. Karavasiloglou N, Pestoni G, Pannen ST, et al. How prevalent is a cancer-protective lifestyle? Adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research cancer prevention recommendations in Switzerland. *Br J Nutr.* 2023;130(5):904-910. doi:10.1017/S0007114522003968

23. Olmedo-Requena R, Lozano-Lorca M, Salcedo-Bellido I, et al. Compliance with the 2018 World Cancer Research Fund/American Institute for Cancer Research Cancer Prevention Recommendations and Prostate Cancer. *Nutrients.* 2020;12(3):768. doi:10.3390/nu12030768
24. Solans M, Romaguera D, Gracia-Lavedan E, et al. Adherence to the 2018 WCRF/AICR cancer prevention guidelines and chronic lymphocytic leukemia in the MCC-Spain study. Cancer Epidemiol. 2020;64:101629. doi:10.1016/j.canep.2019. 101629
25. Hawrysz I, Wadolowska L, Slowinska MA, Czerwinska A, Golota JJ. Lung Cancer Risk in Men and Compliance with the 2018 WCRF/AICR Cancer Prevention Recommendations. *Nutrients.* 2022;14(20):4295. doi:10.3390/nu14204295
26. Peng Y, Bassett JK, Hodge AM, et al. Adherence to 2018 WCRF/AICR cancer prevention recommendations and risk of cancer: the Melbourne Collaborative Cohort Study. *Cancer Epidemiol Biomarkers Prev.* Published online November 9, 2023. doi:10.1158/1055-9965.EPI-23-0945
27. Jacobs I, Taljaard-Krugell C, Wicks M, et al. Adherence to cancer prevention recommendations is associated with a lower breast cancer risk in black urban South African women. *Br J Nutr.* 2022;127(6):927-938. doi:10.1017/S0007114521001598
28. Huang H, Sun P, Zou K, He J, Zhang Y. Current situation and prospect of primary prevention of cancer in China. *Chin J Oncol.* 2022;44(9):942-949. (in Chinese). doi: 10.3760/cma.j.cn112152-20220209-00083
29. Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention. *China Food Composition 2002.* Beijing: Peking University Medical Press; 2002
30. Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention. *China Food Composition 2004.* Beijing: Peking University Medical Press; 2004
31. Collaborative Group for Data Compilation and Analysis on Obesity Issues in China. Predictive values of body mass index and waist circumference to risk factors of related diseases in Chinese adult population. *Chinese Journal of Epidemiology*. 2002;23(1):5-10. (in Chinese).
32. Zhang G, Li Y, Li L, et al. A study on health literacy level and its influencing factors among urban and rural residents in China, 2021. *Chin. J. Health Educ*. 2024;40(5):387-400. (in Chinese).
33. Miao J, Wu X. Urbanization, socioeconomic status and health disparity in China. *Health & Place*. 2016;42:87–95. doi: 10.1016/j.healthplace.2016.09.008
34. Rubin M. Job-Related Determinants of Unhealthy Lifestyles. *J Occup Environ Med*. 2018;60(12):e647-e655. doi:10.1097/JOM.0000000000001456
35. The Lancet. Health in the age of disinformation. *The Lancet*. 2025;405(10474):173. doi:10.1016/S0140-6736(25)00094-7
36. Subramaniam M, Devi F, AshaRani PV, et al. Barriers and facilitators for adopting a healthy lifestyle in a multi-ethnic population: A qualitative study. *PLoS One*. 2022;17(11):e0277106. doi:10.1371/journal.pone.0277106
37. Hardcastle SJ, Hancox J, Hattar A, et al. Motivating the unmotivated: how can health behavior be changed in those unwilling to change? *Front Psychol*. 2015;6:835. doi:10.3389/fpsyg.2015.00835
38 Chen P, Li F, Harmer P. Healthy China 2030: moving from blueprint to action with a new focus on public health. *The Lancet Public Health*. 2019;4(9):e447. doi:10.1016/S2468-2667(19)30160-4
39. Espina C, Herrero R, Sankaranarayanan R, et al. Toward the World Code Against Cancer. *J Glob Oncol*. 2018;4:1-8. doi:10.1200/JGO.17.00145
40. Yang Q, Van Stee SK. The Comparative Effectiveness of Mobile Phone Interventions in Improving Health Outcomes: Meta-Analytic Review. *JMIR Mhealth Uhealth.* 2019;7(4):e11244. doi:10.2196/11244

The BRICS HEALTH JOURNAL 2025; 2 (1): 53-68

journal homepage: https://www.bricshealthjournal.com
https://doi.org/10.47093/3034-4700.2025.2.1.53-68

ORIGINAL ARTICLE

Multi-targeted molecular docking, pharmacokinetic analysis, and drug-likeness evaluation of alkaloids for anti-diabetic drug development

Asfaw Meressa, Biruktawit Girma, Temesgen Negassa, Gashaw Nigussie, Mewded Kasahun, Negessa Abdisa, Sintayehu Ashenef, Samson Taye, Dereilo Bekere Belitibo, Zelalem Animaw, Wakuma Wakene, Baye Akele, Milkyas Endale

Asfaw Meressa, MSc, Researcher, Traditional and Modern Medicine Research and Development Directorate, In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia

Biruktawit Girma, MSc, Researcher, Traditional and Modern Medicine Research and Development In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia

Temesgen Negassa, MSc, Researcher, Traditional and Modern Medicine Research and Development In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia

Gashaw Nigussie, MSc, Associate researcher, Traditional and Modern Medicine Research and Development In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia; Communicable and Non-Communicable Research In silico and Modern Medicine Research Division, Armauer Hansen Research Institute, P.O.Box 1005, P. O. Box 1005, Addis Ababa, Ethiopia

Mewded Kasahun, MSc, Researcher, Traditional and Modern Medicine Research and Development In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia

Negessa Abdisa, MSc, Researcher, Traditional and Modern Medicine Research and Development In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia

Sintayehu Ashenef, MSc, Associate researcher, Traditional and Modern Medicine Research and Development In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia

ORCID numbers: Asfaw Meressa 0000-0002-5301-9923; Biruktawit Girma 0000-0002-0235-4158; Temesgen Negassa 0009-0005-3755-188X; Gashaw Nigussie 0000-0002-7758-6367; Mewded Kasahun 0009-0008-1718-050X; Negessa Abdisa 0009-0000-2123-3960; Sintayehu Ashenef 0000-0002-5924-4005; Samson Taye 0000-0003-4108-0484; Dereilo Bekere Belitibo 0009-0002-8809-9780; Zelalem Animaw 0000-0001-9270-5558; Wakuma Wakene 0000-0002-1100-5718; Baye Akele 0009-0003-2557-5353; Milkyas Endale 0000-0002-5301-9923

Correspondence to: Asfaw Meressa, MSc, Researcher, Traditional and Modern Medicine Research and Development Directorate, In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI).
Address: P. O. Box 1005, Addis Ababa, Ethiopia
E-mail: asfawmeresa03@gmail.com
Milkyas Endale, PhD, Professor, Lead researcher, Traditional and Modern Medicine Research and Development Directorate, In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI).
Address: P. O. Box 1005, Addis Ababa, Ethiopia
E-mail: milkyas.endale@ahri.gov.et

Contributors: Asfaw Meressa: Conducted all phases of this article, including conceptualization, research, writing, and final revisions. Biruktawit Girma: Conducted all phases of this article, including conceptualization, research, writing, and final revisions. Temesgen Negassa: Contributed in data curation, formal analysis, methodology, validation, visualization, writing original draft, review and editing. Gashaw Nigussie: Conducted all phases of this article, including conceptualization, research, writing, and final revisions. Mewded Kasahun: Contributed in data curation, formal analysis, review and editing. Negessa Abdisa: Contributed in data curation, formal analysis, review and editing. Sintayehu Ashenef: Contributed in data curation, formal analysis, methodology, visualization, review and editing. Samson Taye: Contributed in

data curation, formal analysis, visualization, writing original draft, review and editing. Dereilo Bekere Belitibo: Conducted all phases of this article, including conceptualization, research, writing, and final revisions. Zelalem Animaw: Contributed in data curation, formal analysis, methodology, validation, visualization, review and editing. Wakuma Wakene: Contributed in data curation, formal analysis, methodology, validation, visualization, writing original draft, review and editing. Baye Akele: Contributed in data curation, formal analysis, methodology, validation, visualization, review and editing. Milkyas Endale: Contributed in conceptualization, data curation, formal analysis, methodology, validation, visualization, review and editing. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Informed consent statement: Not required

Funding: This research was funded by Armauer Hansen Research Institute (AHRI).

Competing interests: The authors declare no conflict of interest.

Ethical approval: This research work is in accordance with the ethical certificate of approval (Protocol Number: EPHI-IRB-363-2021) issued from Ethiopian Public health Institute Institutional Review Board (EPHI-IRB) for the Protocol Title-Development of Ethiopian Herbal Medicine Database for Computer Aided Drug Discovery (CADD) and Data Repository of Ethnomedicine, Pre-clinical and Clinical Data.

Data sharing: Not applicable.

Acknowledgments: We appreciate Armauer Hansen Research Institute (AHRI) for supporting the research.

Manuscript source: Unsolicited manuscript

Country/Territory of origin: Ethiopia

Received: 23.01.2025
Accepted: 25.03.2025
Date of publication: 19.05.2025

Samson Taye, MSc, Researcher, Communicable and Non-Communicable Research In silico and Modern Medicine Research Division, Armauer Hansen Research Institute, P.O.Box 1005, P. O. Box 1005, Addis Ababa, Ethiopia

Dereilo Bekere Belitibo, MSc, Lecturer, Associate researcher, Traditional and Modern Medicine Research and Development In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia

Zelalem Animaw, PhD, Assistant professor, Researcher, Department of Biomedical Sciences, College of Health Sciences, Debre Tabor University, P.O.Box 272, Debre Tabor, Ethiopia; Traditional and Modern Medicine Research and Development In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia

Wakuma Wakene, MSc, Lecturer, Associate researcher, Traditional and Modern Medicine Research and Development In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia

Baye Akele, MSc, Assistant professor, Associate researcher, Traditional and Modern Medicine Research and Development In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia

Milkyas Endale, PhD, Professor, Lead researcher, Traditional and Modern Medicine Research and Development Directorate, In silico and Modern Medicine Research Division, Armauer Hansen Research Institute (AHRI), P. O. Box 1005, Addis Ababa, Ethiopia

ABSTRACT

Background: Diabetes mellitus is a global health challenge, particularly in low-income regions, leading to severe complications. Plant-derived alkaloids offer potential as alternatives to conventional therapies. The aim of this study is to evaluate 31 selected alkaloids for antidiabetic drugs development.

Materials and methods: Molecular docking, pharmacokinetics and drug-likeness analyses were performed for 31 alkaloids. Four standard drugs (epalrestat, metformin, acarbose, glibenclamide) and four targets (aldose reductase, adenosine monophosphate-activated protein kinase, α-glucosidase, protein tyrosine phosphatase 1B) were used for computational simulations.

Results: Molecular docking revealed that alkaloids mahanimbine (-11.5 kcal/mol), echinulin (11.3 kcal/mol), coptisine (-10.9 kcal/mol), and groenlandicine (-9.7 kcal/mol) have substantial binding affinities against aldose reductase compared to epalrestat (-9.3 Kcal/mol). In contrast to metformin (-4.8 kcal/mol), coptisine, echinulin, sanguinarine, and groelandicine showed superior binding affinities against adenosine monophosphate-activated protein kinase. In comparison to acarbose (-8.4 Kcal/mol), coptisine (-9.7 Kcal/mol), sanguinarine (-9.3 Kcal/mol), mahanimbine (-8.9 Kcal/mol), and echinulin (-8.9 Kcal/mol) demonstrated better docking scores against α-glucosidase. Jatrorrhizine, coptisine, sanguinarine, mahanimbine and echinuline respectively demonstrated higher binding scores of 8.8, -7.5, -7.5 and -7.2 Kcal/mol against protein tyrosine phosphatase 1B than glibenclamide (-7.0 Kcal/mol). Most alkaloids adhered to Lipinski's rule, except casuarine 6-O-α-glucoside and conophylline. Pharmacokinetics identified pinoline as highly bioavailable and central nervous system penetrant, while conophylline had poor bioavailability.

Conclusion: The study concluded that alkaloids including mahanimbine, echinulin, coptisine, groenlandicine, sanguinarine, and jatrorrhizine show strong binding affinities and favorable pharmacokinetic properties, requiring further *in vitro* and *in vivo* studies for therapeutic validation

Key Words: Diabetes mellitus; molecular docking; alkaloids; pharmacokinetics; antidiabetic therapy

Citation: Meressa A, Girma B, Negassa T, Nigussie G, Kasahun M, Abdisa N, Ashenef S, Taye S, Bekere DB, Animaw Z, Wakene W, Akele B, Endale M. Multi-targeted molecular docking, pharmacokinetic analysis, and drug-likeness evaluation of alkaloids for anti-diabetic drug development. *The BRICS Health Journal.* 2025;2(1):53-68. https://doi.org/10.47093/3034-4700.2025.2.1.53-68

Introduction

Diabetes mellitus (DM) is a chronic condition characterized by elevated blood glucose levels resulting from either insulin deficiency (Type 1) or insulin resistance (Type 2). DM has become a significant global health issue, affecting approximately 463 million people worldwide in 2019, with numbers expected to rise substantially in the coming decades [1]. The impact is particularly severe in low- and middle-income countries, where a significant portion of adults with diabetes reside [2, 3]. The incidence of diabetes has sharply increased in Africa, where healthcare systems are often overstretched, and the World Health Organization (WHO) has labeled it a "silent killer" [4]. In countries like Ethiopia, diabetes prevalence is also on the rise, exacerbating the challenges for healthcare systems, particularly due to the growing number of untreated cases [5]. Diabetes leads to a wide range of both acute and chronic complications, severely affecting quality of life [6]. Chronic hyperglycemia can result in microvascular complications (e.g., retinopathy, nephropathy, and neuropathy) as well as macrovascular problems, such as cardiovascular disease.

The primary treatment options for DM currently include insulin therapy, oral hypoglycemic drugs such as metformin, sulfonylureas, and thiazolidinediones, as well as newer medications like sodium-glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists [7]. While these treatments are effective in controlling blood glucose levels and reducing the risk of complications, they are not without limitations. Prolonged use of insulin and oral hypoglycemics can lead to undesirable side effects, including weight gain, hypoglycemia, and gastrointestinal issues[1]. Additionally, the cost and accessibility of these treatments pose significant challenges, particularly in resource-limited regions like Sub-Saharan Africa, where the prevalence of diabetes is increasing [8].

Diabetes results from β-cell failure and insulin resistance, affecting critical processes like insulin secretion and carbohydrate absorption [9]. Key proteins such as glucokinase, adenosine monophosphate-activated protein kinase (AMPK), and 11β-hydroxysteroid dehydrogenase are involved in diabetes development [10]. While conventional treatments like anti-diabetic drugs and lifestyle changes are available, they often come with side effects and questionable efficacy. As a result, there is growing interest in natural products, particularly plant-derived compounds such as alkaloids, flavonoids, and glycosides, known for their therapeutic potential in managing diabetes [11]. Alkaloids, in particular, have shown promise in improving glucose metabolism, insulin sensitivity, and oxidative stress management [12, 13].

[1] Feingold KR. Oral and Injectable (Non-Insulin) Pharmacological Agents for the Treatment of Type 2 Diabetes. [Updated 11.09.2024]. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Accessed on 16.01.2025. https://www.ncbi.nlm.nih.gov/books/NBK279141.

The search for natural product-derived molecules for diabetes treatment has led to an increasing focus on medicinal plants and their bioactive constituents [14, 15]. Computational drug discovery has become a vital tool in identifying and optimizing small molecules, enabling the prediction of drug-target interactions. These methods are crucial for diabetes management, as they help identify compounds that can regulate blood sugar levels effectively [16]. Molecular modeling and virtual screening techniques have revolutionized drug discovery, making it possible to efficiently evaluate large numbers of compounds for their therapeutic potential [16].

Recent advancements in computational approaches, such as protein-ligand docking and absorption, distribution, metabolism, excretion, and toxicity (ADMET) property prediction, are accelerating drug development. The incorporation of ADMET analysis early in the discovery process helps predict the pharmacokinetic and toxicity profiles of compounds, reducing the risk of clinical failure [17, 18]. This study aims to conduct molecular docking and analyze the pharmacokinetic properties, drug-likeness, and toxicity profiles of selected alkaloids based on their lethal dose (LD50) values and anti-diabetic potential.

Materials and methods

Alkaloids selection

Scientific studies have shown that alkaloids exhibit pharmacological activity against type 2 diabetes mellitus (T2DM) [19]. Alkaloids such as berberine, catharanthine, vindoline, and vindolinine have been reported for their anti-hyperglycemic effects [19, 20]. The selection criteria for molecular docking study against T2DM targets included alkaloids with documented *in vitro* and *in vivo* glucose antidiabetic activity, inhibitory potential against the selected targets, and interactions with other key T2DM-related targets. The antioxidant properties of the compounds were also considered [21]. The alkaloids of plant origin [19, 21-36] selected for the current computational study was indicated below (Fig. 1).

Selection of target proteins and standard drugs

Target proteins and standard drugs were selected based on their established roles in glucose metabolism and diabetes management, as well as their recognition in treatment guidelines. These targets were chosen for their diverse mechanisms of action, allowing for a multifaceted approach to diabetes treatment. AMPK is a key regulator of cellular energy homeostasis, and its activation by metformin, a first-line therapy recommended by the American Diabetes Association and WHO guidelines, promotes enhanced glucose uptake and fatty acid oxidation, improving insulin sensitivity [37]. Aldose reductase, involved in diabetic complications, is targeted by epalrestat to reduce sorbitol accumulation [38]. Alpha-glucosidase is inhibited by acarbose, a drug recommended for its efficacy in slowing carbohydrate absorption and mitigating glucose spikes [39].

Protein preparation

Protein preparations were performed following established protocols [40]. The crystal structures of selected human target proteins were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (https://www.rcsb.org/): aldose reductase (PDB ID: 2R24), alpha glucosidase (PDB ID: 8YIE), AMPK (PDB: 4YEE), and protein tyrosine phosphatase 1B (PDB ID: 7LEO). The 3D crystal structures were imported into Biovia Discovery Studio Visualizer 2021, where water

FIG 1. Structures of selected alkaloids

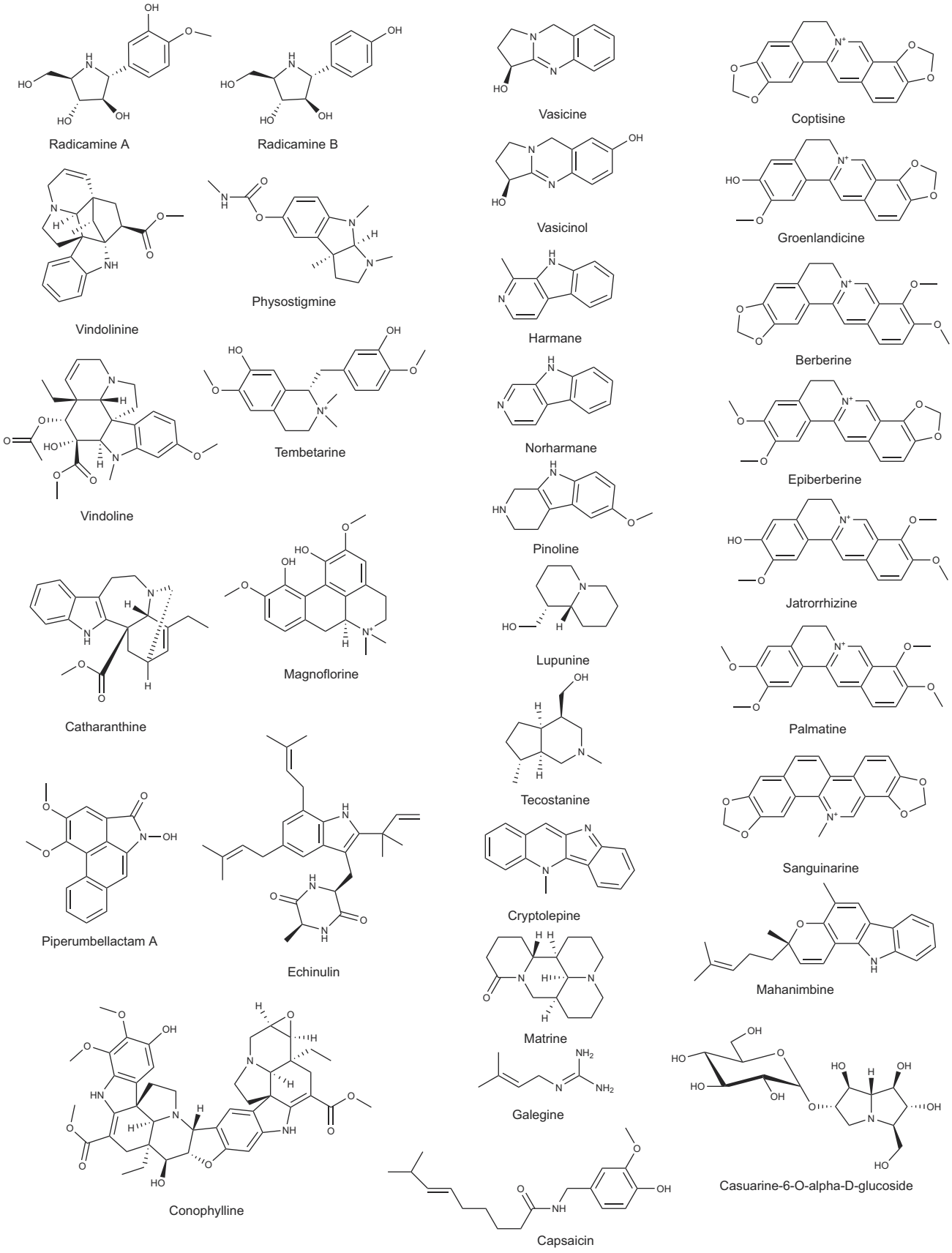


Table. Grid-box coordinates for all targets.

Targets	x-dimension	y-dimension	z-dimension	x-center	y-center	z-center
2R24	40	40	40	16.618583	-7.134417	15.260125
4YEE	40	40	40	80.858534	-5.804455	12.281989
8YIE	40	40	40	-37.153167	32.035500	-4.817833
7LEO	40	40	40	-1.942455	-0.591773	56.110909

molecules, heteroatoms, and any complexes bound to the receptor molecules were removed. For site-specific molecular docking, ligand groups were selected from the co-crystallized protein structures, defined, and binding sites identified by extracting the x, y, and z coordinates from the structure-based design site spheres. Active sites were determined by analyzing the binding interactions between ligands and receptors with molecular docking performed at the active sites of the prepared proteins. The grid box was created using a docking simulation with dimensions of 40x40x40 Å along the x, y, and z axes, respectively, and a grid point spacing of 0.375 Å. The dimensions of the structure-based design site sphere for each target protein are listed in Table, with corresponding x, y, and z values. Finally, polar hydrogens were added to ensure proper ionization of the amino acid residues.

Ligand preparation

The 2D chemical structures of selected alkaloids and standard drugs were retrieved from the pubchem database and downloaded in PDB format. Alkaloids whose 2-D structures were not retrieved from the PUBCHEM were generated using the ChemOffice tool (ChemDraw 16.0), and the files were subsequently converted to PDB format using the Open Babel toolbox. These structures were then converted into three-dimensional forms, with polar hydrogens and charges at physiological pH 7.4 added. Energy minimization and optimization were performed using the Merck Molecular Force Field 94 (MMFF94) force field in ChemBio3D Ultra 13.0 (PerkinElmer, 2011) with the molecular modeling algorithm. Additionally, Gasteiger charges were assigned to the three-dimensional ligand structures, and the files were converted to pdbqt format using AutoDock Tools. The energy minimization process was continued until the root mean square deviation (RMSD) gradient reached 0.01 kcal/mol, ensuring that the structures achieved their lowest energy conformations. Once minimized to their lowest energy states, the ligand molecules were saved in PDB format. These minimized ligands were then used as input for AutoDock Vina to perform molecular docking simulations, assessing their binding affinity and interactions with the target proteins [40-42].

Molecular docking

Molecular docking predicts the binding affinity of ligand molecules by assessing protein-ligand interactions and estimating the scoring function based on geometry. Computational molecular docking studies were performed to investigate the binding patterns of selected alkaloids (Figure 1), along with the crystal structures of the chosen target proteins. The crystal structures of the human target proteins – aldose reductase (PDB ID: 2R24), alpha glucosidase (PDB ID: 8YIE), AMPK (PDB: 4YEE), and protein tyrosine phosphatase 1B (PDB ID: 7LEO) – were retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/). Using AutoDock Vina 4.2.6 (MGLTools 1.5.7), a software suite in the Discovery Studio 2021 Client (a program for interactive visualization and analysis of molecular structures

and related data), the interactions and binding affinities of the ligands with the selected target proteins were evaluated. Binding affinity was explored using the View Dock tool. The final results were analyzed and visualized using Discovery Studio 2021 Client, with bound ligands as the standard. Visualization of protein-ligand interactions reveals the number of interactions and the active residues responsible for significant binding at the active sites of the selected targets [42]. Epalrestat, glibenclamide, metformin, and acarbose were used as standards.

Drug-likeness and ADMET prediction

SwissADME (http://www.swissadme.ch/) web servers were used to predict the drug-likeness and ADME profiles of the selected alkaloids, while toxicity analysis was conducted using the ProTox-II web server (http://tox.charite.de/protox_II). The predicted drug-likeness and ADMET profiles of the compounds were obtained by uploading the simplified molecular-input line-entry system formats of each alkaloid's structure to the respective web servers [43-45].

Results and discussion

Drug likeness properties and ADMET

The failure rate in drug development across preclinical to clinical stages exceeds 90%. Even among drug candidates that successfully complete clinical trials, approximately 90% face failure in later stages [46]. Contributing factors to clinical trial failures include suboptimal pharmacokinetic profiles, lack of clinical efficacy, unmanaged toxicity, and poor drug-like properties. Among these, the most critical issue arises from the failure of investigational drugs in late-stage clinical development. Therefore, it is essential to evaluate the ADMET properties early in the drug development process to mitigate these risks [47]. Currently, numerous available *in silico* drug-likeness and ADMET prediction tools supplement experimental data and are becoming increasingly indispensable in the context of efforts to minimize animal testing [48, 49].

Physicochemical properties are critical parameters that influence both the pharmacodynamics and pharmacokinetic profiles of drug candidates. In this study, Lipinski's and Veber's rules were employed to evaluate the drug-likeness properties of the selected alkaloids. According to this rule, a molecule is considered drug-like if its molecular weight (MW) is < 500 Da, the number of hydrogen bond donors (HBD) is <5, the number of hydrogen bond acceptors (HBA) is <10, and the octanol-water partition coefficient (Log P) is <5. Compounds that do not violate more than two of these parameters are deemed to possess drug-like properties [50]. Molecules that violate fewer than two criteria are expected to demonstrate favorable gastrointestinal absorption. In this study, casuarine 6-O-α-glucoside and conophylline, violate Lipinski's Rule of Five. It is important to note that Lipinski's rule is not applicable to amino acids and sugars. Although casuarine 6-O-α-glucoside does not adhere to Lipinski's Rule of Five, it contains a sugar moiety, which facilitates its absorption upon oral administration. This underscores that the Lipinski Rule of Five is not an absolute criterion, and drug discovery should extend beyond these parameters [51, 52]. One of the key molecular descriptors in Lipinski's Rule is molecular weight. According to the rule, compounds with a molecular weight greater than 500 Da are less likely to traverse the paracellular pores of the intestinal epithelium. All alkaloids, except for conophylline (MW = 794.89 Da), possess an acceptable molecular weight for potential bioavailability.

Lipophilicity is a crucial physicochemical parameter in the development of new drug entities, as it significantly influences drug-likeness properties and the pharmacokinetic profile. It is one of the key factors in Lipinski's Rule of Five [53]. All alkaloids included in this study exhibit optimal MlogP values (less than 4.5) or ClogP values below 5, indicating that these compounds possess favorable lipophilicity. Furthermore, lipophilicity plays a significant role in the binding affinity of these alkaloids to receptors at the drug's target site, as many receptors are inherently lipophilic [54].

While lipophilicity plays a critical role in the pharmacokinetic profile of a drug, it is essential that a new drug entity does not exhibit excessive lipophilicity. Highly lipophilic compounds may have poor solubility in the gastrointestinal tract (GIT), thus hindering absorption [55]. An ideal drug entity demonstrates optimal absorption when there is a balanced hydrophilic-lipophilic balance, meaning the compound should possess sufficient lipophilicity to permeate biological membranes while remaining polar enough to dissolve in the GIT.

Solubility characteristics are classified as insoluble when the value is more negative than -10. The solubility ranges from poorly soluble to highly soluble, with values between -10 and 0 indicating varying degrees of solubility. Poorly soluble compounds exhibit values between -10 and -6, moderately soluble compounds range from -6 to -4, soluble compounds fall between -4 and -2, very soluble compounds are in the range of -2 to 0, and highly soluble compounds have values greater than 0. In this study, all alkaloids exhibit acceptable solubility, with the exception of mahanimbine, echinulin, and conophylline, which display poor water solubility. To further evaluate drug-likeness and oral bioavailability, Veber's Rule is employed. This rule predicts the drug-likeness and oral bioavailability of new drug entities by considering the number of rotatable bonds and topological polar surface area (TPSA) as key determinants.

With respect to TPSA, Veber and colleagues suggest that for optimal oral bioavailability, compounds should have a TPSA of ≤140 $Å^2$ [56]. Molecules exceeding this threshold are generally considered less favorable as drug candidates due to poor absorption and distribution characteristics. The TPSA values of most alkaloids in this study fall within the acceptable range, indicating their druggability. However, three compounds – cryptolepine (17.82 $Å^2$), casuarine 6-O-α-glucoside (183.54 $Å^2$), and conophylline (163.82 $Å^2$) violate Veber's rule with respect to this molecular descriptor. The presence of polar functional groups plays a crucial role, not only in determining the pharmacokinetic profile but also in influencing the pharmacodynamic properties of drug-like molecules. These polar functional groups interact with receptor residues, which are critical for effective binding [57].

The second key variable in Veber's rule is the number of rotatable bonds (NRB), which reflects a compound's flexibility. A compound is predicted to have favorable oral bioavailability if its NRB does not exceed 10, as excessive flexibility may hinder absorption [56]. All selected alkaloids possess fewer than 10 rotatable bonds, suggesting favorable bioavailability. As the number of rotatable bonds increases, however, toxicity risks also rise as excessive flexibility allows a compound to adopt multiple conformations, increasing its potential to bind with various receptors [56, 58].

Molecular docking

Molecular docking analysis of various alkaloids against aldose reductase (PDB: 2R24) revealed a range of binding affinities and represented in Supplement A (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-a). The most promising candidates, mahanimbine and echinulin, exhibited strong

docking scores of -11.5 kcal/mol and -11.3 kcal/mol, respectively, suggesting that these alkaloids form stable interactions with this enzyme and are potential inhibitors of it. Coptisine (-10.9 kcal/mol) and berberine (-9.5 kcal/mol) also demonstrated potent binding affinities, aligning with their previously reported bioactivity against aldose reductase, making them suitable for further exploration as therapeutic agents. Moderate binding affinity was observed for standard medication epalrestat (-9.3 kcal/mol) and alkaloids harmane (-9.3 kcal/mol) and sanguinarine (-8.8 kcal/mol), suggesting potential aldose reductase inhibitors with less potency, potentially contributing to therapeutic strategies. Weaker docking scores were recorded for alkaloids such as galegine (-5.8 kcal/mol), vindoline (-5.8 kcal/mol), and lupinine (-5.8 kcal/mol), which showed the least favorable interactions with aldose reductase. Despite their lower binding affinity, these compounds could still hold therapeutic potential, possibly in combination therapies or as adjuncts to more potent inhibitors. Overall, the study highlights the diverse binding profiles of alkaloids, with mahanimbine, echinulin, and coptisine being the most promising candidates for further investigation as aldose reductase inhibitors, while moderate and weaker binders may still be valuable in specific therapeutic contexts.

The molecular docking analysis of various ligands against AMPK (PDB: 4YEE), represented in Supplement B (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-b), revealed a range of binding affinities, suggesting differences in their potential to interact with the enzyme's active site. Among the most promising compounds, coptisine exhibited the highest docking score of -10.1 kcal/mol, indicating a strong binding affinity to AMPK. Other notable high-affinity ligands included sanguinarine (-9.5 kcal/mol), groenlandicine (-9.4 kcal/mol), and echinulin (-9.7 kcal/mol), which also showed robust binding interactions, positioning them as potential candidates for further investigation in the development of AMPK-targeted therapies.

Alkaloids such as vindolinine (-7.6 kcal/mol), physostigmine (-7.3 kcal/mol), harmane (-7.5 kcal/mol), and jatrorrhizine (-8.8 kcal/mol) exhibited binding affinity, suggesting they may be useful in modulating AMPK activity. Pinoline (-6.7 kcal/mol) and berberine (-8.3 kcal/mol) also demonstrated moderate affinity, indicating that these compounds may still have potential as AMPK modulators, potentially in combination with other agents to enhance therapeutic outcomes. These findings highlight the broader potential of these alkaloids in regulating AMPK activity and warrant further investigation.

Metformin exhibited a docking score of -4.8 kcal/Mol, which is lower than the tested alkaloids though metformin has been extensively studied and demonstrated to activate AMPK *in vivo* through mechanisms not solely reliant on direct binding affinity. The modest docking score reflects the complexity of metformin's action, which involves multiple pathways, including inhibition of mitochondrial complex I and alteration of cellular energy status, rather than a direct, strong binding interaction with the AMPK active site. Therefore, despite the lower docking score, metformin remains a valuable therapeutic agent, and its clinical efficacy in AMPK activation supports its continued use and exploration in metabolic disease management. Overall, this study identified coptisine, sanguinarine, and echinulin as the most promising candidates for AMPK modulation, while metformin's weaker binding score does not diminish its established therapeutic relevance in clinical practice.

Molecular docking analysis of various ligands against alpha-glucosidase (PDB: 8YIE), represented in Supplement C (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-

annex-c), revealed a broad spectrum of binding affinities, reflecting the potential of different compounds as inhibitors of this enzyme. Among the alkaloids studied, coptisine exhibited the highest docking score of -9.7 kcal/mol. Conophylline (-9.5 kcal/mol), sanguinarine (-9.3 kcal/mol), mahanimbine (-8.9 kcal/mol), and echinulin (-8.9 kcal/mol), showed promising docking scores.

Other alkaloids demonstrated moderate binding affinities to alpha-glucosidase, with docking scores ranging from -7.0 to -8.7 kcal/mol. These include radicamine A (-8.7 kcal/mol), acarbose (-8.4 kcal/mol), groenlandicine (-8.6 kcal/mol), berberine (-8.5 kcal/mol), and piperumbellatm A (-8.5 kcal/mol). These compounds exhibited favorable binding, indicating their potential as moderate alpha-glucosidase inhibitors. Acarbose, a known alpha-glucosidase inhibitor used in clinical practice, shows a docking score of -8.4 kcal/mol, which aligns with its established therapeutic effect, validating the docking results.

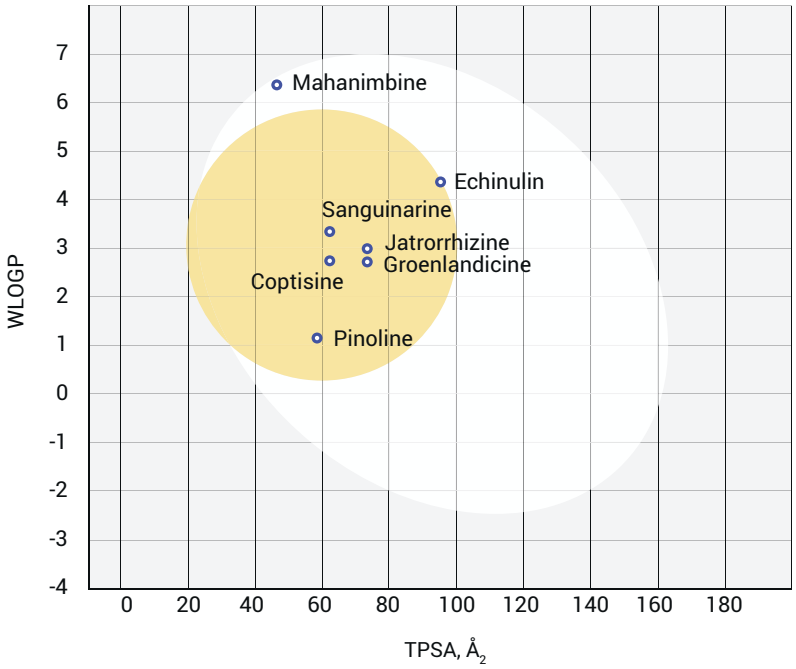
Some compounds showed weaker docking scores, suggesting less effective binding to alpha-glucosidase. These include radicamine B (-5.5 kcal/mol), galegine (-4.9 kcal/mol), and lupinine (-5.3 kcal/mol), which demonstrated the least favorable interactions with the enzyme. Although these compounds exhibited weaker binding, their potential utility might lie in other therapeutic contexts or in combination therapies with stronger inhibitors. Additionally, the lower binding affinities observed in these compounds may be attributed to factors such as weaker molecular interactions or alternative mechanisms of action that were not captured by the docking analysis alone.

Molecular docking of various ligands against protein tyrosine phosphatase 1B (PDB:7LEO), represented in Supplement D (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-d), revealed varying degrees of binding affinity. Jatrorrhizine, coptisine, sanguinarine, mahanimbine, and echinulin, all with strong binding properties, are promising alkaloids for further investigation in managing type 2 diabetes. They may offer valuable therapeutic potential in regulating postprandial glucose levels through protein tyrosine phosphatase 1B inhibition. The alkaloids radicamine A (-6.6 kcal/mol), radicamine B (-5.5 kcal/mol), vindolinine (-6.3 kcal/mol), and groenlandicine (-6.8 kcal/mol) displayed moderate binding, suggesting potential in combination therapies or glucose regulation adjuncts. Weaker docking scores were observed for galegine, tecostanine, and capsaicin, indicating less favorable interactions with this protein.

Comprehensive analysis of the drug likeness and ADMET prediction 31 alkaloids, represented in Supplement E https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-e), revealed favorable characteristics for drug development among which coptisine, sanguinarine, and jatrorrhizine exhibited promising drug-like properties, including optimal molecular weight, moderate lipophilicity, and strong hydrogen bonding potential. These compounds are well-suited for further development as alpha-glucosidase inhibitors. The bioavailability score of all alkaloids, represented in Supplement F (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-f), except casuarine 6-O-α-glucoside and conophyline, was consistently 0.55, suggesting moderate systemic availability [59].

Cryptolepine, jatrorrhizine, and epiberberine have been identified as CYP450 inhibitors, particularly targeting CYP3A4 and CYP1A2, which may influence the metabolism of co-administered drugs. In contrast, compounds such as palmatine, pinoline, and radicamine A were found to exhibit minimal interactions with major cytochrome P450 enzymes, making them favorable in terms of lower drug-drug interaction risks. The blood-

FIG 2. BOILED-egg model of selected alkaloids.



Note: Molecules penetrating blood-brain barrier are located inside the yellow ellipse, molecules absorbed in intestine are located in white ellipse. WLOGP - Wildman-Crippen 1-octanol-water partition coefficient, TPSA - topological polar surface area.

brain barrier (BBB) permeant data suggested that harmane and sanguinarine can cross BBB. Although for antidiabetic applications, this may not be relevant unless central nervous system (CNS) effects are desired. Alkaloids with high gastrointestinal absorption, moderate lipophilicity, and minimal metabolic interference such as vindolinine, coptisine, and sanguinarine present the most promise.

Gastrointestinal absorption and brain access are two pharmacokinetic behaviors crucial to estimate at various stages of the drug discovery processes. To this end, the Brain Or IntestinaL Estimate D permeation method (BOILED-Egg) is proposed as an accurate predictive model that works by computing the lipophilicity and polarity of small molecules. In this study, seven alkaloids were selected based on their binding affinity and pharmacokinetic property. Mahanimbine, found at the border of the egg white (white eclipse), is likely hydrophilic, which suggests limited BBB penetration. This positioning indicates that mahanimbine may exert its effects peripherally. Echinulin, positioned at the boundary between the yolk and the egg white (yolk eclipse), appears to have a dual solubility profile, allowing it to interact with both aqueous and lipid environments. This suggests that echinulin may have the potential to cross the BBB due to its ability to interact with lipid-rich membranes. Sanguinarine, jatrorhizine, groenlandicine, coptisine, and pinoline, located predominantly in the lipid-rich yolk are lipophilic, are able to cross BBB and GIT. Their lipophilic nature positions them as promising agents for both central and peripheral therapeutic effects in the management of diabetes (Fig. 2).

The *in silico* toxicity analysis of the selected compounds, represented in Supplement G (supplementary materials on the journal website https://doi.org/10.47093/3034-4700.2025.2.1.53-68-annex-g), provided valuable insights into their potential toxicological risks, highlighting critical safety considerations for their future applications. The data included predicted LD_{50} values, identifying various toxicity targets, such

as enzymes, receptors, and physiological systems. Physostigmine and capsaicin, categorized as class 1 and class 2, respectively, exhibited low LD_{50} values (2 mg/kg and 47 mg/kg), indicating high toxicity and posing significant risks at low doses. These compounds require careful consideration when exploring therapeutic applications, particularly in populations with sensitivities to neurotoxic or respiratory effects. In contrast, catharanthine and casuarine, classified as class 5, exhibited much higher LD_{50} values (2100 mg/kg and 3500 mg/kg), which suggest a relatively safer profile, although other toxicological endpoints should still be examined.

One of the most significant findings from the analysis was the extensive prediction of interactions with specific toxicity targets, which helped to identify potential risks associated with the compounds. Cryptolepine, vindolinine, and harman exhibited high probabilities for neurotoxicity, respiratory toxicity, and immunotoxicity suggesting that these compounds could adversely affect the nervous system, respiratory function, and immune response. Cryptolepine (Class 4, LD_{50}=1190 mg/kg) showed high probabilities for respiratory toxicity (0.98) and neurotoxicity (0.87), underscoring its potential to cause organ damage at elevated doses.

Neurotoxicity was a common concern across several compounds such as vindolinine, palmatine, and groenlandicine where interactions with neural pathways were predicted with high probabilities. The potential for CNS toxicity emphasizes the need for careful evaluation of these compounds in neurological contexts. Further research is needed to investigate these compounds' CNS effects and their ability to cross the BBB, as indicated by high BBB penetration probabilities.

High probability for mutagenicity for harmane and norharmane suggest these compounds may cause genetic damage, which could potentially lead to cancerous growths. The long-term use of such compounds should be approached cautiously, particularly if they are to be considered for therapeutic purposes. Sanguinarine and capsaicin, with interactions at the estrogen receptor ligand binding domain and aromatase suggest the potential for disrupting hormone signaling pathways, which could lead to adverse effects in both male and female reproductive systems. Cryptolepine, vindolinine, and magnoflorine were predicted to affect environmental organisms with moderate to high probabilities. Given their potential to enter the ecosystem, either through waste, runoff, or environmental contamination, the environmental risks posed by these compounds should not be underestimated. Further studies are necessary to assess their biodegradability, persistence in the environment, and potential to accumulate in non-target organisms.

In silico toxicity profiling of the alkaloids, has provided valuable predictive information regarding their safety and potential risks. While some compounds showed promising safety profiles with higher LD_{50} values and lower toxicity target probabilities, others displayed significant toxicity risks that require further experimental validation. This analysis underscores the importance of combining computational toxicity predictions with *in vivo* studies to obtain a more comprehensive understanding of the risks associated with these compounds.

Conclusion and recommendation

The docking study indicated mahanimbine, echinulin, and coptisine inhibit aldose reductase, and coptisine, sanguinarine, and echinulin significantly modulate AMPK activity, regulate blood glucose levels. Similarly, the alkaloids coptisine, sanguinarine, and mahanimbine exhibited favorable

binding against α-glucosidase and jatrorrhizine showing high binding affinity for tyrosine phosphatase 1B. Pharmacokinetic evaluations also uncovered most alkaloids conformed to Lipinski's Rule of Five, indicating favorable oral bioavailability, with some showing optimal lipophilicity. However, some alkaloids, mahanimbine, echinulin, and conophylline, showed poor water solubility, which may limit their clinical applicability and warrants further optimization. Most compounds had favorable TPSA values.

The pharmacokinetic evaluation indicated that pinoline exhibited excellent oral bioavailability and CNS penetration, while conophylline demonstrated poor bioavailability. Toxicity analysis identified cryptolepine and vindolinine as high-risk compounds for neurotoxicity and hepatotoxicity, necessitating further investigation. Despite these concerns, several alkaloids demonstrated favorable ADMET profiles, positioning them as promising drug leads for diabetes treatment. Sanguinarine, jatrorhizine, groenlandicine, coptisine, and pinoline, located predominantly in the lipid-rich yolk part of the boiled egg model, suggesting these alkaloids are lipophilic, making them ideal candidates for BBB penetration and efficient GI absorption.

Thus, further studies are recommended that mahanimbine, echinulin, coptisine, groenlandicine, sanguinarine, and jatrorrhizine be prioritized for further experimental studies, including *in vitro* and *in vivo* testing. These compounds demonstrated strong binding to key diabetes-related targets and exhibited favorable pharmacokinetic properties, making them viable candidates for antidiabetic drug development. The promising drug-like properties of these alkaloids suggest that they could serve as the foundation for developing novel anti-diabetic therapies, offering alternative treatment options for managing diabetes and its associated complications.

References

1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157:107843. doi:10.1016/j.diabres.2019.107843.
2. Dunachie S, Chamnan P. The double burden of diabetes and global infection in low and middle-income countries. *Trans R Soc Trop Med Hyg.* 2019;113(2):56-64. doi:10.1093/trstmh/try124.
3. Liu J, Bai R, Chai Z, et al. Low- and middle-income countries demonstrate rapid growth of type 2 diabetes: an analysis based on Global Burden of Disease 1990-2019 data. *Diabetologia.* 2022;65(8):1339-1352. doi:10.1007/s00125-022-05713-6.
4. Azevedo MJ. The State of Health System(s) in Africa: Challenges and Opportunities. In: Azevedo MJ. Historical Perspectives on the State of Health and Health Systems in Africa, Volume II. *Palgrave Macmillan Cham.* 2017;1-73.
5. Zekewos A, Loha E, Egeno T, et al. Prevalence of Diabetes Mellitus and Associated Factors in Southern Ethiopia: A Community Based Study. *Ethiop J Health Sci.* 2018;28(4):451-460. doi:10.4314/ejhs.v28i4.11.
6. Papatheodorou K, Banach M, Bekiari E, et al. Complications of Diabetes 2017. *J Diabetes Res*. 2018;2018:3086167. doi:10.1155/2018/3086167.
7. Ganesan K, Rana MBM, Sultan S. Oral Hypoglycemic Medications. In: *StatPearls*. Treasure Island (FL): StatPearls. 2023.
8. Adachi T, El-Hattab AW, Jain R, et al. Enhancing Equitable Access to Rare Disease Diagnosis and Treatment around the World: A Review of Evidence, Policies, and Challenges. *Int J Environ Res Public Health*. 2023;20(6):4732. doi:10.3390/ijerph20064732.
9. Hameed I, Masoodi SR, Mir SA, et al. Type 2 diabetes mellitus: From a metabolic disorder to an inflammatory condition. *World J Diabetes.* 2015;6(4):598-612. doi:10.4239/wjd.v6.i4.598.

10. Damián-Medina K, Salinas-Moreno Y, Milenkovic D, et al. In silico analysis of antidiabetic potential of phenolic compounds from blue corn (Zea mays L.) and black bean (Phaseolus vulgaris L.). *Heliyon.* 2020;6(3):e03632. doi:10.1016/j.heliyon.2020.e03632.
11. Elkhalifa AEO, Al-Shammari E, Adnan M, et al. Development and Characterization of Novel Biopolymer Derived from Abelmoschus esculentus L. Extract and Its Antidiabetic Potential. *Molecules.* 2021;26(12):3609. doi:10.3390/molecules26123609.
12. Amssayef A, Eddouks M. Alkaloids as Promising Agents for the Management of Insulin Resistance: A Review. *Curr Pharm Des.* 2023;29(39):3123-3136. doi:10.2174/0113816128270340231121043038.
13. Gutiérrez-Grijalva EP, Contreras L, Emus-Medina A, Heredia JB. Plant Alkaloids with Antidiabetic Potential. In: Chen H, Zhang M. *Structure and Health Effects of Natural Products on Diabetes Mellitus*. Springer Singapore; 2021:251-266.
14. Blahova J, Martiniakova M, Babikova M, et al. Pharmaceutical Drugs and Natural Therapeutic Products for the Treatment of Type 2 Diabetes Mellitus. *Pharmaceuticals (Basel).* 2021;14(8):806. doi:10.3390/ph14080806.
15. Shanmugam KR, Shanmugam B, Subbaiah GV, et al. Medicinal Plants and Bioactive Compounds for Diabetes Management: Important *Advances in Drug Discovery. Curr Pharm Des.* 2021;27(6):763-774. doi:10.2174/1381612826666200928160357.
16. Sliwoski G, Kothiwale S, Meiler J, Lowe EW Jr. Computational methods in drug discovery. *Pharmacol Rev.* 2013;66(1):334-95. doi:10.1124/pr.112.007336.
17. Wu F, Zhou Y, Li L, et al. Computational Approaches in Preclinical Studies on Drug Discovery and Development. *Front Chem.* 2020;8:726. doi:10.3389/fchem.2020.00726.
18. Agu PC, Afiukwa CA, Orji OU, et al. Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. *Sci Rep*. 2023;13(1):13398. doi:10.1038/s41598-023-40160-2.
19. Behl T, Gupta A, Albratty M, et al. Alkaloidal Phytoconstituents for Diabetes Management: Exploring the Unrevealed Potential. Molecules. 2022;27(18):5851. doi:10.3390/molecules27185851.
20. Sharma S, Sharma A, Gupta U (2021) Molecular Docking studies on the Anti-fungal activity of Allium sativum (Garlic) against Mucormycosis (black fungus) by BIOVIA discovery studio visualizer 21.1.0.0. *Ann Antivir Antiretrovir.* 2021;5(1):028-032. doi:10.17352/aaa.000013
21. Rahman N, Muhammad I; Gul-E-Nayab; et al. Molecular Docking of Isolated Alkaloids for Possible α-Glucosidase Inhibition. *Biomolecules.* 2019;9(10):544. doi:10.3390/biom9100544.
22. Ragab FA, Yahya TA, El-Naa MM, Arafa RK. Design, synthesis and structure-activity relationship of novel semi-synthetic flavonoids as antiproliferative agents. *Eur J Med Chem.* 2014;82:506-20. doi:10.1016/j.ejmech.2014.06.007.
23. O'Boyle NM, Banck M, James CA, et al. Open Babel: An open chemical toolbox. *J Cheminform*. 2011;3:33. doi:10.1186/1758-2946-3-33.
24. Tiong SH, Looi CY, Hazni H, et al. Antidiabetic and antioxidant properties of alkaloids from Catharanthus roseus (L.) G. *Don. Molecules.* 2013;18(8):9770-84. doi:10.3390/molecules18089770.
25. Alam S, Sarker MMR, Sultana TN, et al. Antidiabetic Phytochemicals From Medicinal Plants: Prospective Candidates for New Drug Discovery and Development. *Front Endocrinol (Lausanne).* 2022;13:800714. doi:10.3389/fendo.2022.800714.
26. Salehi B, Ata A, V Anil Kumar N, et al. Antidiabetic Potential of Medicinal Plants and Their Active Components. Biomolecules. 2019;9(10):551. doi:10.3390/ biom9100551.
27. Aba, PE, Asuzu, IU. Mechanisms of actions of some bioactive anti-diabetic principles from phytochemicals of medicinal plants: A review. Indian Journal of Natural *Products and Resources.* 2018; 9:85-96.
28. Sharma R, Bolleddu R, Maji JK, et al. In-Vitro α-amylase, α-glucosidase Inhibitory Activities and In-Vivo Anti-Hyperglycemic Potential of Different Dosage Forms of Guduchi (Tinospora Cordifolia [Willd.] Miers) Prepared With Ayurvedic Bhavana Process. *Front Pharmacol.* 2021;12:642300. doi:10.3389/fphar.2021.642300.

29. Seal S, Kar S, Pal S, et al., Alkaloids of Natural Origin with Promising Anti-Diabetic Properties. In: Odoh UE, Tijani H, Egbuna C. *Advances in Pharmacognosy and Phytochemistry of Diabetes.* Intelligentsia publishing service; 2024:61-83.
30. Meng FC, Wu ZF, Yin ZQ, et al. Coptidis rhizoma and its main bioactive components: recent advances in chemical investigation, quality evaluation and pharmacological activity. *Chin Med.* 2018;13:13. doi:10.1186/s13020-018-0171-3.
31. Gao H, Huang YN, Gao B, et al J. Inhibitory effect on α-glucosidase by Adhatoda vasica Nees. *Food Chem.* 2008;108(3):965-72. doi:10.1016/j.foodchem.2007.12.002.
32. Abd El-Wahab AE, Ghareeb DA, Sarhan EE, et al. In vitro biological assessment of Berberis vulgaris and its active constituent, berberine: antioxidants, anti-acetylcholinesterase, anti-diabetic and anticancer effects. *BMC Complement Altern Med*. 2013;13:218. doi:10.1186/1472-6882-13-218.
33. Bonaccini C, Chioccioli M, Parmeggiani C et al., Synthesis, biological evaluation and docking studies of casuarine analogues: effects of structural modifications at ring B on inhibitory activity towards glucoamylase. *Eur. J. Org. Chem.* 2010: 5574-5585. https://doi.org/10.1002/ejoc.201000632.
34. Muema FW, Nanjala C, Oulo MA, Wangchuk P. Phytochemical Content and Antidiabetic Properties of Most Commonly Used Antidiabetic Medicinal Plants of Kenya. *Molecules*. 2023;28(20):7202. doi:10.3390/molecules28207202.
35. Dineshkumar B, Mitra A, Mahadevappa M. Antidiabetic and hypolipidemic effects of mahanimbine (carbazole alkaloid) from Murraya koenigi (rutaceae) leaves. *Int J of Phytomed.* 2010;2(1):22-30.
36. Dirir AM, Daou M, Yousef AF, Yousef LF. A review of alpha-glucosidase inhibitors from plants as potential candidates for the treatment of type-2 diabetes. *Phytochem Rev.* 2022;21(4):1049-1079. doi:10.1007/s11101-021-09773-1.
37. Goel S, Singh R, Singh V, et al. Metformin: Activation of 5' AMP-activated protein kinase and its emerging potential beyond anti-hyperglycemic action. *Front Genet.* 2022;13:1022739. doi:10.3389/fgene.2022.1022739.
38. Madeswaran A, Umamaheswari M, Asokkumar K, et al., Discovery of potential aldose reductase inhibitors using in silico docking studies. *Orient Pharm Exp Med.* 2012;12:157-161. doi:10.1007/s13596-012-0065-3
39. Jhong CH, Riyaphan J, Lin SH, et al. Screening alpha-glucosidase and alpha-amylase inhibitors from natural compounds by molecular docking in silico. *Biofactors*. 2015;41(4):242-51. doi:10.1002/biof.1219.
40. Müller A, Neukam M, Ivanova A, et al. A Global Approach for Quantitative Super Resolution and Electron Microscopy on Cryo and Epoxy Sections Using Self-labeling Protein Tags. *Sci Rep.* 2017;7(1):23. doi:10.1038/s41598-017-00033-x.
41. Olaokun OO, Manonga SA, Zubair MS, et al. Molecular Docking and Molecular Dynamics Studies of Antidiabetic Phenolic Compound Isolated from Leaf Extract of Englerophytum magalismontanum (Sond.) T.D.Penn. *Molecules.* 2022;27(10):3175. doi:10.3390/molecules27103175.
42. Sulaiman NAS, Azman MFSN, Aluwi MFFM, et al. Stereospecific α-glucosidase inhibition, kinetics, and molecular docking studies on isolated diastereomeric alkaloids from Uncaria longiflora. *Results Chem.* 2025;13:101926. doi:10.1016/j.rechem.2024.101926
43. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: a webserver for the prediction of toxicity of chemicals. *Nucleic Acids Res*. 2018;46(W1):W257-W263. doi:10.1093/nar/gky318.
44. Demir C, İstifli ES. Docking-based virtual screening, ADMET, and network pharmacology prediction of anthocyanidins against human alpha-amylase and alpha-glucosidase enzymes as potential antidiabetic agents. *International Journal of Plant Based Pharmaceuticals*, 2022;2(2):271-283.
45. Pires DE, Blundell TL, Ascher DB. pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. *J Med Chem*. 2015;58(9):4066-72. doi:10.1021/acs.jmedchem.5b00104.
46. Sun D, Gao W, Hu H, Zhou S. Why 90% of clinical drug development fails and how to improve it? *Acta Pharm Sin B.* 2022;12(7):3049-3062. doi:10.1016/j.apsb.2022.02.002.

47. Dulsat J, López-Nieto B, Estrada-Tejedor R, Borrell JI. Evaluation of Free Online ADMET Tools for Academic or Small Biotech Environments. *Molecules.* 2023;28(2):776. doi:10.3390/molecules28020776.
48. Suhandi C, Wilar G, Narsa AC, et al. Updating the Pharmacological Effects of α-Mangostin Compound and Unraveling Its Mechanism of Action: A Computational Study Review. *Drug Des Devel Ther.* 2024;18:4723-4748. doi:10.2147/DDDT.S478388.
49. Venkatraman V. FP-ADMET: a compendium of fingerprint-based ADMET prediction models. *J Cheminform.* 2021;13(1):75. doi:10.1186/s13321-021-00557-5.
50. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev.* 2012;64(Supplement):4-17.
51. Lipinski CA. Lead-and drug-like compounds: the rule-of-five revolution. Drug Discov. *Today Technol.* 2004;1(4):337-341.
52. Benet LZ, Hosey CM, Ursu O, Oprea TI. BDDCS, the Rule of 5 and drugability. *Adv Drug Deliv Rev.* 2016;101:89-98. doi:10.1016/j.addr.2016.05.007.
53. Tafreshi NK, Kil H, Pandya DN, et al. Lipophilicity Determines Routes of Uptake and Clearance, and Toxicity of an Alpha-Particle-Emitting Peptide Receptor Radiotherapy. *ACS Pharmacol Transl Sci*. 2021;4(2):953-965. doi:10.1021/acsptsci.1c00035.
54. Morak-Młodawska B, Jeleń M, Martula E, Korlacki R. Study of Lipophilicity and ADME Properties of 1,9-Diazaphenothiazines with Anticancer Action. *Int J Mol Sci*. 2023;24(8):6970. doi:10.3390/ijms24086970.
55. Kadela-Tomanek M, Jastrzębska M, Marciniec K, et al. Lipophilicity, Pharmacokinetic Properties, and Molecular Docking Study on SARS-CoV-2 Target for Betulin Triazole Derivatives with Attached 1,4-Quinone. *Pharmaceutics.* 2021;13(6):781. doi:10.3390/pharmaceutics13060781.
56. Veber DF, Johnson SR, Cheng HY, et al. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem.* 2002;45(12):2615-23. doi:10.1021/jm020017n.
57. Martin JL, Esmaeili H, Manuel RC, et al. Pharmacokinetics/Pharmacodynamics of Dabigatran 75 mg Twice Daily in Patients With Nonvalvular Atrial Fibrillation and Severely Impaired Renal Function. *J Cardiovasc Pharmacol Ther.* 2018;23(5):399-406. doi:10.1177/1074248418769167.
58. Asano D, Takakusa H, Nakai D. Oral Absorption of Middle-to-Large Molecules and Its Improvement, with a Focus on New Modality Drugs. *Pharmaceutics.* 2023;16(1):47. doi:10.3390/pharmaceutics16010047.
59. Arnott JA, Planey SL. The influence of lipophilicity in drug discovery and design. *Expert Opin Drug Discov.* 2012;7(10):863-75. doi:10.1517/17460441.2012.714363.

SECHENOV UNIVERSITY
LIFE SCIENCES