INPLASY

Glycogen Synthase Kinase-3 (GSK-3) in Human Papillomavirus (HPV)-Driven Cancers: A Scoping Review Protocol

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ADMINISTRATIVE INFORMATION

Support - FRGS/1/2024/SKK10/UPNM/02/1.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202630112

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 March 2026 and was last updated on 30 March 2026.

INTRODUCTION

Review question / Objective Review question: What role does GSK-3 play in the molecular mechanisms underlying HPV-driven carcinogenesis?
Objective: To systematically map and synthesize current peer-reviewed evidence regarding the expression, regulation, and therapeutic targeting of GSK-3 (α and β isoforms) across in vitro, in vivo, and clinical models of HPV-associated malignancies.

Background Human papillomavirus (HPV) is a highly contagious virus transmitted primarily via skin-to-skin contact during sexual activity. Persistent infection with high-risk HPV subtypes acts as a primary oncogenic driver for a significant subset of malignancies, including cervical, penile, vulvar, vaginal, anal, laryngeal, oral, and oropharyngeal cancers. Mechanistically, HPV drives oncogenesis primarily through the expression of the viral E6 and E7 oncoproteins. These oncoproteins disrupt normal host cell cycle regulation by promoting the degradation of crucial tumor suppressor proteins, namely p53 and the retinoblastoma protein (pRb). Consequently, key host signaling networks including phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), nuclear factor kappa B (NF-kappaB), and canonical Wnt/β-catenin pathways are disrupted.
Within these disrupted networks, glycogen synthase kinase-3 (GSK-3) emerges as a critical regulatory node. GSK-3, a serine/threonine kinase with two isoforms (GSK-3α and GSK-3β), has emerged as a pivotal regulator of diverse cellular processes, including metabolism, cell cycle progression, apoptosis, and DNA repair. Intriguingly, GSK-3 exhibits context-dependent roles in cancer biology—acting as a tumor suppressor in some settings while promoting oncogenesis in others.

Rationale Recent studies demonstrate that GSK-3 interacts directly with HPV E6 and E7 oncoproteins, leading to the disruption of host signaling pathways that govern cell proliferation

and viral genome maintenance. Despite its critical role in viral oncogenesis, existing literature predominantly isolates its focus to individual tumor types. To date, no comprehensive review has mapped the exact mechanisms and regulatory roles of GSK-3 across the entire spectrum of HPV-driven cancers. Therefore, this scoping review aims to address this knowledge gap by systematically charting the available in vitro, in vivo, and clinical evidence. By elucidating how GSK-3 is modulated within specific HPV-driven oncogenic environments, this review seeks to provide an integrated overview of its functional status and evaluate its potential as an emerging therapeutic target in HPV-associated malignancies.

METHODS

Strategy of data synthesis Search strategy:
A comprehensive literature search will be conducted across four major electronic databases: PubMed, Scopus, ScienceDirect, and Web of Science. The search will be performed from database inception to December 2025.
Key Search Terms: Combinations of “Glycogen synthesis kinase-3” (AND synonyms), “Human papillomavirus” (AND synonyms including "HPV"), and “Cancer” (AND synonyms including "Malignancy", "Neoplasms").

Eligibility criteria Participants/Population:
Models or patients representing cancers driven by HPV infection. This includes HPV-derived cell lines (e.g., HeLa, SiHa, CaSki), animal models (e.g., HeLa xenografts), and clinical patient tumor cohorts (e.g., cervical cancer, head and neck cancer, anogenital cancers). Studies strictly evaluating HPV-negative cell lines or non-HPV-driven cancers will be excluded.

Concept:
The role, expression, activity, or regulatory mechanism of GSK-3α and GSK-3β isoforms within the context of HPV-driven malignant transformation. This includes the evaluation of pharmacological or genetic interventions (e.g., natural chemopreventive agents, siRNA) that modulate GSK-3 expression or phosphorylation states.

Context:
Molecular and clinicopathological insights derived from peer-reviewed experimental and observational evidence. Comparisons will include baseline versus post-intervention GSK-3 activity, or GSK-3 profiles in neoplastic tissues versus adjacent normal tissues.

Source of evidence screening and selection
Data selection and extraction will follow the PRISMA-ScR guidelines.
Screening: Unique records will be screened in two phases by two independent reviewers (TNAN and NACR)
Phase 1: Title and abstract screening based on predefined inclusion/exclusion criteria
Phase 2 Full-text screening of eligible studies.
Any disagreement between the two reviewers will be resolved by discussion or by consulting a third reviewer (RZF).

Data management A structured extraction form will capture: (1) Study demographics (author, year, location, design); (2) HPV subtype; (3) Intervention details (compound, concentration, duration); (4) GSK-3 isoform studied; (5) Molecular targets and signaling pathways; and (6) Key findings regarding GSK-3 expression/activity and cellular responses.

Main outcome:
1) GSK-3 expression levels (total protein/mRNA) and functional activity
2) Clinicopathological outcomes associated with GSK-3 status (e.g., tumor grade, FIGO stage, survival times)

Additional outcome:
Modulation of key downstream oncogenic targets and cellular responses linked to GSK-3 activity.

Reporting results / Analysis of the evidence
Data will be synthesized qualitatively. Extracted studies will be categorized by study design (in vitro, in vivo, clinical) to identify trends and will be described narratively.
As this is a scoping review aimed at charting the breadth of available literature and mapping molecular mechanisms, a formal risk of bias assessment or quality appraisal of the included studies will not be performed, in accordance with standard scoping review frameworks (e.g., Arksey and O'Malley).

Presentation of the results Key findings will be narratively summarized and visually mapped, highlighting the functional cross-talk between GSK-3 and upstream/downstream signaling pathways in HPV-driven carcinogenesis. Tabular summaries will be provided to contrast clinical expression profiles with experimental intervention outcomes.

Language restriction Only studies published in English will be considered due to resource limitation.

Country(ies) involved Malaysia.

Keywords Glycogen Synthase Kinase-3; Human Papillomavirus (HPV); HPV-driven cancers; Scoping Review.

Contributions of each author

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