International Journal of Otorhinolaryngology and Head and Neck Surgery
Widiantari IAA et al. Int J Otorhinolaryngol Head Neck Surg. 2026 Apr;12(2):309-313
http://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937
DOI: https://dx.doi.org/10.18203/issn.2454-5929.ijohns20260656

Review Article

The role of bamboo shoots derived flavonoids as Epstein-Barr virus inhibitors in nasopharyngeal carcinoma

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Received: 13 January 2026
Accepted: 09 February 2026

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ABSTRACT

Epstein-Barr virus (EBV) is a ubiquitous oncogenic virus that infects humans and is strongly associated with various malignancies, including nasopharyngeal carcinoma (NPC), Hodgkin lymphoma, and B-cell lymphomas. One of the major challenges in the management of EBV-associated diseases is the virus's ability to establish latency and evade host immune surveillance. Conventional treatments such as chemotherapy and radiotherapy are often unable to specifically target latent EBV reservoirs, highlighting the need for complementary therapeutic approaches. Bamboo shoots, a traditional dietary component, contain a variety of flavonoid compounds that have been shown to possess diverse biological activities, including antiviral and anticancer effects. This article aims to review the potential of flavonoid compounds found in bamboo shoots as anti-EBV agents in NPC based on evidence from previous studies. The review methodology involved a comprehensive search of scientific publications from reputable databases. The findings indicate that flavonoids such as luteolin, apigenin, and quercetin present in bamboo shoots exert inhibitory effects on the EBV life cycle by suppressing viral reactivation from the latent to the lytic phase, downregulating the expression of EBV latent proteins (LMP1 and LMP2A), and inducing apoptosis in EBV-infected cells. In conclusion, flavonoids derived from bamboo shoots demonstrate potential for development as adjuvant therapeutic agents in NPC by targeting EBV infection; however, further studies are required to establish their clinical efficacy.

Keywords: Epstein-Barr virus, Nasopharyngeal carcinoma, Hodgkin lymphoma, B-cell lymphoma

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignancy with a high prevalence in Indonesia, particularly in the eastern regions of the country. Unlike other head and neck cancers, NPC exhibits a remarkably strong association with Epstein-Barr virus (EBV) infection. More than 95% of NPC cases in endemic areas are associated with EBV, in which the virus plays a pivotal role in tumorigenesis through the expression of latent viral proteins, including latent membrane protein 1 (LMP1), latent membrane protein 2A (LMP2A), and Epstein-Barr nuclear antigen 1 (EBNA1).[1,2]

EBV, also known as human herpesvirus 4 (HHV-4), infects more than 90% of the global adult population. Following primary infection, the virus typically persists in a latent state within B lymphocytes, establishing lifelong persistent infection. Under certain conditions, reactivation of the virus from the latent to the lytic phase may occur. This process, in combination with the expression of latent viral proteins such as LMP1, LMP2A, and EBNA, can promote cellular proliferation and malignant transformation. Based on this evidence, EBV has been classified as a group 1 human carcinogen.[3]

Diseases associated with EBV, such as NPC, are highly dependent on the presence and reactivation of the virus.

The standard treatment for advanced-stage NPC is chemoradiotherapy; however, recurrence rates remain high, which is thought to be attributable to the persistence of therapy-resistant tumor cells and latent viral reservoirs.[4,5] Therefore, the development of therapeutic strategies that specifically target EBV and EBV-infected cells represents an urgent medical need in the management of NPC.

Bamboo shoots have long been consumed as a traditional food source in various Asian countries. Beyond their nutritional value, bamboo shoots are rich in phytochemical compounds, particularly flavonoids.[6] Numerous studies have reported the biological activities of flavonoids, including antioxidant, anti-inflammatory, anticancer, and antiviral effects. Several flavonoids present in bamboo shoots, such as luteolin, apigenin, and quercetin, have been investigated for their potential activity against EBV. Their ability to modulate multiple cellular signaling pathways and to target different stages of the viral life cycle makes these bioactive compounds promising candidates for the treatment of complex diseases, including those associated with EBV.[7] This article reviews the molecular mechanisms and therapeutic potential of flavonoids derived from bamboo shoots as anti-EBV agents in NPC.

PHYTOCHEMICAL COMPOSITION OF BAMBOO SHOOTS

Bamboo shoots are functional food materials rich in bioactive phytochemical compounds, particularly phenolic antioxidants and flavonoids, as well as phytosterols and dietary fiber.[8] These constituents confer substantial potential benefits in supporting cardiovascular health, digestive function, and the prevention of chronic diseases. When appropriately processed to eliminate antinutritional factors, bamboo shoots represent a highly valuable addition to a healthy dietary pattern.[9]

Phenolic compounds and flavonoids (major antioxidants)

Phenolic compounds and flavonoids represent the most important phytochemical groups in bamboo shoots and are responsible for most of their antioxidant activity. These compounds can neutralize free radicals that induce oxidative stress and cellular damage. Phenolic acids identified in bamboo shoots include gallic acid, caffeic acid, chlorogenic acid, cinnamic acid, and ferulic acid. Ferulic acid is known for its anti-inflammatory and neuroprotective properties. Flavonoids such as flavones, flavonols, and flavanones also contribute significantly to the biological activity of bamboo shoots, playing key roles in anti-inflammatory, anti-allergic, and anticancer effects. Collectively, these compounds have been shown to combat premature aging, prevent degenerative diseases including cancer, diabetes, and cardiovascular disease. It also can reduce inflammatory processes.[6]

Phytosterols plant derived cholesterol

Phytosterols are steroid compounds with chemical structures similar to cholesterol particularly beta sitosterol as well as campesterol and stigmasterol. These compounds are known to reduce serum cholesterol levels by competing with dietary cholesterol during intestinal absorption thereby lowering circulating levels of low-density lipoprotein cholesterol. Beta sitosterol has also been reported to alleviate symptoms associated with benign prostatic hyperplasia.[9,10]

Lignans and cellulose bioactive fiber

Lignans are a type of insoluble dietary fiber that also function as phytoestrogens whereas cellulose constitutes the primary structural fiber component. Both compounds contribute to gastrointestinal health by preventing constipation and maintaining intestinal integrity. In addition, they act as prebiotics serving as substrates for beneficial probiotic bacteria in the colon. These fibers also support body weight regulation by promoting prolonged satiety. Several lignans such as those identified in bamboo shoots of Gigantochloa verticillata have been reported to exhibit cytotoxic activity against the cancer cells.[8]

Saponin

Saponins are glycosidic compounds that produce foam when shaken in aqueous solutions. These compounds have cholesterol lowering properties through the formation of non absorbable complexes with cholesterol in the intestine. Saponins also exhibit antimicrobial activity against bacteria and fungi. In addition, they possess immunomodulatory potential by stimulating immune system responses.[10]

Oxalic acid and cyanogenic glycosides antinutritional factors

Bamboo shoots also contain several compounds considered antinutritional factors because they may interfere with mineral absorption or exhibit potential toxicity when consumed raw and in excessive amounts. These compounds include oxalic acid and cyanogenic glycosides. Oxalic acid is capable of binding minerals such as calcium and iron thereby reducing their absorption. Excessive intake may contribute to kidney stone formation in susceptible individuals. Cyanogenic glycosides such as taxiphyllin are compounds that can release toxic hydrogen cyanide when raw bamboo shoots are cut or crushed. However, this risk can be effectively mitigated through appropriate processing methods. Soaking and thorough boiling prior to consumption allow cyanide compounds to dissolve and volatilize rendering bamboo shoots safe for consumption.[7] The following table presents the phytochemical composition of bamboo shoots and their general health benefits.

Table 1: Composition of bamboo shoots and general health benefits.

Phytochemical components	Main health benefits
Phenolic compounds and flavonoids	Antioxidant anti-inflammatory anticancer cardiovascular and neuroprotective effects.
Phytosterols	Reduction of low-density lipoprotein cholesterol and support of prostate health.
Lignans and cellulose	Digestive health prebiotic effects body weight control and potential anticancer activity.
Saponins	Antimicrobial activity cholesterol lowering effects and immunomodulatory properties.
High dietary fiber content	Improved bowel function glycemic control and cholesterol reduction.
High potassium content	Regulation of blood pressure.

Proper processing of bamboo shoots is essential to maximize their health benefits and ensure safety for consumption. It is important to note that bamboo shoots should never be consumed raw. The hard outer layers should first be removed, followed by thin slicing of the shoots and soaking them in water for a minimum of two hours, with overnight soaking being preferable. Subsequent processing involves boiling the bamboo shoots in a large volume of water for at least twenty to thirty minutes without covering the pot. This step allows potentially toxic cyanide gas to evaporate. The first boiling water should be discarded, after which the shoots may be boiled once more to further ensure safety and to reduce bitterness.[6]

FLAVONOID CONTENT IN BAMBOO SHOOTS

Bamboo shoots contain a wide range of flavonoid compounds that function as natural antioxidants. Several flavonoids identified in bamboo shoots include luteolin, apigenin, quercetin, catechin, vitexin, and isovitexin.[11]

The concentration and composition of these flavonoids vary depending on bamboo species, shoot maturity, growth conditions, and processing methods. Previous studies have reported that bamboo shoots from the species Dendrocalamus asper contain a total flavonoid content of 45.2 mg QE per 100 g of fresh weight.[6] The following diagram illustrates the role of flavonoid compounds as anti-virus agents.

Table 2: Flavonoid compounds with reported anti-virus activity.

Flavonoid compound or class	Source	Reported anti-virus activity based on research
Flavones general class	Various plant sources including bamboo	Serve as the basic structural framework of many bioactive flavonoids
Luteolin (Imran et al)[12]	Celery thyme bamboo shoots	Reported to inhibit replication of influenza A virus coxsackie B virus and SARS CoV
Apigenin (Salehi et al)[13]	Chamomile parsley bamboo shoots	Demonstrates activity against hepatitis B virus herpes simplex virus and influenza virus
Quercetin (Kashyap et al)[14]	Apples onions bamboo shoots	Extensively studied compound shown to inhibit influenza virus rhinovirus hepatitis C virus and SARS CoV 2 in *in vitro* studies
Catechins such as EGCG (Wong et al)[15]	Green tea	Widely recognized for strong anti-virus properties particularly against influenza virus and HIV
Saponins not classified as flavonoids but present in bamboo shoots (Gupta et al)[16]	Bamboo shoots ginseng	May function as immune adjuvants by enhancing immune responses against viral antigens

MECHANISMS OF FLAVONOIDS IN ANTIVIRAL ACTIVITY

Flavonoids represent a highly diverse group of compounds that have been extensively investigated for their antiviral properties. The antiviral mechanisms of flavonoids generally include inhibition of viral entry into host cells. Several flavonoids are able to bind to viral surface proteins such as spike proteins or to host cell receptors such as ACE2. By masking or altering these structures, flavonoids can prevent viral attachment and subsequent entry into host cells, thereby disrupting the initial stage of infection.[17]

Another important mechanism involves inhibition of viral replication. After viral entry, replication is required for viral propagation. Flavonoids can inhibit key viral enzymes necessary for replication, including viral proteases and RNA dependent RNA polymerase. These enzymes function as essential machinery for viral genome duplication, and their inhibition effectively suppresses the production of new viral particles.[18]

In addition, flavonoids exert immunomodulatory effects by enhancing both innate and adaptive immune responses. They are known to stimulate the production of endogenous antiviral mediators such as interferons and to regulate cytokine responses, thereby preventing excessive inflammatory reactions or cytokine storms that are commonly associated with severe viral infections.[11]

PATHOGENESIS OF NPC AND THE ROLE OF EBV

EBV infects nasopharyngeal epithelial cells and persists in a latent state. Viral proteins expressed during the latent phase, particularly LMP1, play a critical role in malignant transformation through multiple mechanisms, including activation of the NF kappa B and AP 1 signaling pathways, inhibition of apoptosis, induction of angiogenesis, and modulation of immune responses. The presence of Epstein Barr virus in NPC cells is not only involved in tumor initiation but is also associated with disease progression and response to therapy.[1]

EBV LIFE CYCLE AND PATHOGENESIS AS POTENTIAL TARGETS FOR FLAVONOID INTERVENTION

Understanding of EBV life cycle is essential for identifying potential points of flavonoid intervention. Lytic phase represents productive stage during which virus replicates its DNA and generates new virion particles. Potential targets during this phase include viral enzymes such as DNA polymerase and immediate early transactivators including Zta BZLF1 and Rta BRLF1.[19]

The latent phase is a dormant state in which the viral genome persists within host cells with limited gene expression. Latent proteins including LMP1, LMP2A and EBNA drive oncogenesis by activating pro survival signaling pathways such as NF kappa B PI3K Akt and JAK STAT.[19,20] Flavonoids have the potential to interfere with both the lytic and latent phases of EBV infection. This dual targeting capability represents a significant advantage compared with conventional antiviral agents which typically act only on the lytic phase.

EBV MECHANISMS OF ACTION OF BAMBOO SHOOT FLAVONOIDS IN INHIBITING EBV

Numerous studies have elucidated specific mechanisms by which flavonoids present in bamboo shoots inhibit EBV. One key mechanism involves the suppression of viral reactivation from the latent to the lytic phase, a critical event in EBV associated pathogenesis. Apigenin has been shown to inhibit the promoter activity of the Zta gene BZLF1, which functions as a major transactivator initiating the lytic cycle.[11,14] By suppressing Zta expression, apigenin maintains the virus in a latent state.

Luteolin exhibits a similar inhibitory effect by suppressing the expression of Zta and Rta genes, thereby preventing viral reactivation.[13] In addition, flavonoids are capable of downregulating the expression and function of latent viral proteins. Among these proteins, LMP1 represents the primary oncogenic driver of EBV. Quercetin and apigenin have been reported to reduce LMP1 expression. These compounds inhibit NF kappa B and AP 1 signaling pathways activated by LMP1. By disrupting these survivals and inflammatory signaling pathways, flavonoids promote apoptosis of EBV infected cells and suppress their proliferative capacity.[13,14]

Another important mechanism involves the induction of apoptosis and inhibition of proliferation in EBV infected cells. Flavonoids present in bamboo shoots are capable of inducing apoptosis in EBV infected NPC cells through multiple pathways, including caspase activation, regulation of Bcl 2 family protein expression, and induction of selective oxidative stress. In addition, flavonoids exhibit antiangiogenic properties by suppressing the expression of vascular endothelial growth factor induced by EBV related proteins, thereby inhibiting tumor angiogenesis and disease progression.[21]

Tabel 3: Overview of selected flavonoids and *in vitro* and *in vivo* evidence as anti EBV.

Flavonoids	Source	Mechanism of action of anti-EBV	Research evidence
Apigenin (Wu et al)[17]	Parsley celery chamomile	Inhibition of viral reactivation through suppression of Zta gene transcription	Studies conducted on EBV infected B lymphoma cells and nasopharyngeal epithelial cells
Luteolin (Imran et al)[12]	Celery thyme broccoli	Suppression of Zta and Rta gene expression and reduction of LMP1 expression	Demonstrated ability to inhibit chemically induced EBV reactivation
Quercetin (Liu et al)[20]	Apples onions berries	Inhibition of NF kappa B signaling activated by LMP1 and antioxidant activity	Shown to suppress growth of Raji cells which are EBV positive Burkitt lymphoma cells
EGCG	Green tea	Induction of apoptosis inhibition of LMP1 mediated signaling and suppression of DNA methyltransferase activity	Effective in inhibiting growth of EBV positive NPC C666 1 cells both *in vitro* and *in vivo* using murine models
Fisetin	Strawberries apples grapes	Induction of apoptosis and inhibition of cell migration and invasion	Inhibited NPC cell growth and reduced viability of EBV positive cells

CHALLENGES AND FUTURE PROSPECTS

Despite the highly promising preclinical evidence, several challenges must be addressed. One major limitation is bioavailability, as many flavonoids exhibit low oral bioavailability due to extensive metabolism in the intestine and liver. This limitation necessitates the development of novel formulation strategies, such as nanoemulsions and liposomal delivery systems, to enhance compound stability and improve targeted tissue delivery. Furthermore, since clinical trial evidence in humans remains very limited, further well-designed studies are required to establish the safety and efficacy of specific flavonoids as adjuvant therapies in patients with EBV associated diseases.

CONCLUSION

The body of scientific evidence accumulated to date strongly indicates that flavonoids represent promising multi-target compounds in combating EBV infection and the diseases associated with it. Flavonoids act not only as direct antiviral agents by suppressing viral reactivation, but also as anticancer agents by interfering with oncogenic signaling pathways driven by EBV proteins and by inducing tumor cell death.

Further research, particularly well-designed clinical trials, is critically needed to confirm these preclinical findings and to translate this considerable potential into effective therapeutic applications for patients with NPC and other EBV-associated malignancies. Flavonoid-based approaches offer hope for the development of safer and more specific therapeutic strategies in the future.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Widiantari IAA, Dwi Fatmawati NN, Nuaba IGA, Suanda IK, Lesmana IWL. The role of bamboo shoots derived flavonoids as Epstein-Barr virus inhibitors in nasopharyngeal carcinoma. Int J Otorhinolaryngol Head Neck Surg 2026;12:309-13.