Medical and Health Journal
Volume 6, Issue 1, 2026, pp. 30-39
e-ISSN: 2807-3541
Open Access: https://jos.unsoed.ac.id/index.php/mhj

Antiproliferative and Anti-Inflammatory Effects of *Physalis angulata* L. Extract on Various Human Cancer Cell Lines in Vitro Studies: Systematic Review

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ARTICLE INFO

Article history:
Received July 13, 2026
Revised July 30, 2026
Accepted August 01, 2026
Available online August 20, 2026

Keywords:
Anticancer, Anti-inflammatory, *Physalis angulata* L., Physalin, Withanolide

ABSTRACT

Cancer was a leading cause of mortality worldwide and in Indonesia, with limited access to modern therapies and significant adverse effects associated with chemotherapy. The medicinal plant Physalis angulata L. was investigated as a potential alternative due to its cytotoxic and anti-inflammatory properties against cancer cells. This review aimed to evaluate evidence from studies examining the anticancer potential of isolated compounds from this plant. A systematic search was conducted using PubMed and ScienceDirect databases following PRISMA guidelines, focusing on in vitro studies published within the last ten years. Six studies met the inclusion and exclusion criteria. Data were extracted based on plant parts, isolation methods, tested cell lines, and study outcomes using IC50 values. The results show that all studies produce withanolide fractions through extraction using polar to semi-polar solvents, followed by purification with various chromatographic techniques. The main compounds in Physalis angulata, particularly withanolides such as physalin and physagulide, exhibit moderate to strong anticancer activity across various cancer cell lines (IC_{50} 0.18–21.75 μM) and demonstrate anti-inflammatory effects by inhibiting iNOS and COX-2 production. Physalins increase reactive oxygen species, leading to mitochondrial damage and activation of apoptosis. Several compounds also inhibit key signaling pathways involved in cell survival, including MAPK, JAK/STAT3, Wnt/β-catenin, and Hedgehog pathways. The anti-inflammatory effects occur through inhibition of the NF-κB pathway, resulting in reduced expression of pro-inflammatory mediators. In conclusion, Physalis angulata L. shows promising anticancer and anti-inflammatory potential in vitro, supporting its development as a candidate for future therapeutic applications. Further studies are required to validate these findings in vivo and in clinical settings.

1. INTRODUCTION

Cancer remains a leading cause of morbidity and mortality worldwide and ranks as the second most common cause of death after cardiovascular disease. According to the latest Global Cancer Observatory (GLOBOCAN 2022), approximately 20 million new cancer cases and 9.7 million cancer-related deaths were reported worldwide, and the global cancer burden is expected to continue increasing because of population growth, population ageing, and changes in lifestyle-related risk factors (Bray et al., 2024). Of the 10 million individuals diagnosed each year, nearly 6 million die from cancer. Globally, more than 19.3 million new cases are reported annually, and this number is projected to reach 21 million by 2030 (Bray et al., 2018). Indonesia faces a substantial cancer burden; according to the Global Cancer Observatory (GLOBOCAN) 2022, there were more than 408,000 new cancer cases and over 242,000 cancer-related deaths in the country (Bray et al., 2024; Jenca et al., 2024; Nurulita, 2025). The most prevalent cancer types include breast (16.6%), cervical (9.2%), lung (8.8%), colorectal (8.6%), and liver (5.1%) cancers. Delayed diagnosis, limited access to treatment facilities, and low awareness of early detection contribute significantly to high mortality rates. The increasing incidence is more pronounced in low- and

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middle-income countries, largely due to unhealthy lifestyle factors such as poor diet, smoking, and low physical activity (Bray et al., 2018). These challenges emphasize the urgent need to develop effective, safe, and affordable therapeutic agents that are accessible to a broader population.

Current cancer treatments continue to face several challenges, including limited access to specialized cancer care centers that are not readily available to all populations (Sulaiman et al., 2025). Standard therapeutic approaches include surgery, radiotherapy, chemotherapy, and immunotherapy. Although these modalities have improved survival in many patients, their clinical effectiveness is frequently compromised by systemic toxicity, drug resistance, tumor recurrence, high treatment costs, and limited selectivity toward cancer cells (Jenča et al., 2024; Nurulita, 2025). Chemotherapeutic agents generally act as cytotoxic compounds that interfere with various stages of the cell cycle. Their use is primarily based on the fact that cancer cells tend to proliferate more rapidly than normal cells, making them more susceptible to these agents. However, these drugs are also associated with adverse effects such as nausea, vomiting, mucositis, alopecia, neuropathy, and myelosuppression (Jenča et al., 2024). In addition, most chemotherapeutic agents are non-selective, meaning they damage not only cancer cells but also normal cells that are vulnerable to their toxic effects (Nurulita, 2025). These limitations have stimulated growing interest in medicinal plants as a valuable source of bioactive compounds with multitarget mechanisms and potentially lower toxicity than conventional anticancer agents (Newman & Cragg, 2020; Sulaiman et al., 2025).

Ongoing research continues to explore and refine therapeutic protocols. The use of traditional herbal medicines and medicinal plants has played a significant role in the development of novel anticancer agents. Medicinal plants contain secondary metabolites with cytotoxic activity, antiproliferative activity, proapoptotic activity, and anti-inflammatory activity (Newman & Cragg, 2020). Herbal medicines and plant extracts are generally considered safer and are associated with lower toxicity compared to synthetic chemical agents (Sulaiman et al., 2025; Hasan et al., 2024). Although traditional medicines may also produce side effects, their long-term risks are typically lower than those associated with conventional chemical drugs (Nurulita, 2025). In addition to uncontrolled cell proliferation, chronic inflammation has been recognized as a key hallmark of cancer progression. Persistent activation of inflammatory mediators, including nuclear factor-kappa B (NF-κB), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), cyclooxygenase-2 (COX-2), and signal transducer and activator of transcription-3 (STAT3), promotes tumor initiation, proliferation, angiogenesis, invasion, metastasis, and resistance to apoptosis (Mantovani et al., 2008; Greten & Grivennikov, 2019). Therefore, compounds exhibiting both antiproliferative activity and anti-inflammatory activity may provide greater therapeutic benefits than agents targeting only cancer cell proliferation. Based on these considerations, medicinal plants possessing multiple biological activities deserve further investigation as potential anticancer candidates.

The Indonesian Ministry of Health encourages the use of traditional medicinal plants as complementary therapies alongside modern treatment or as alternative options in cancer management. One plant with considerable potential that grows widely in Indonesia is ciplukan (Physalis angulata L.). This species belongs to the Solanaceae family and is distributed across Southeast Asia, the Americas, and Africa. It has been traditionally used to treat fever, inflammation, and infections (Meira et al., 2022). Various parts of the plant, including the shoots, leaves, fruits, stems, seeds, and roots, are utilized (Nurulita, 2025). Experimental studies have reported that its bioactive compounds, particularly withanolides such as physalin and physagulide, exhibit strong biological activities, including antiproliferative activity, cytotoxic activity, anti-inflammatory activity, and immunomodulatory effects (Sun et al., 2016; Gao et al., 2017; Meng et al., 2019). The anticancer activity of Physalis angulata has been associated with increased Reactive Oxygen Species (ROS) production, induction of apoptosis, and inhibition of the NF-κB signaling pathway (Wang, 2018; Meira et al., 2022). Furthermore, previous studies have demonstrated that Physalis angulata regulates apoptosis through caspase-3 activation, modulation of Bax/Bcl-2 expression, activation of p53 signaling, induction of cell-cycle arrest at the G0/G1 or G2/M phases, and inhibition of PI3K/Akt and MAPK signaling pathways, thereby suppressing cancer cell proliferation and inflammatory responses (Sun et al., 2016; Gao et al.,

2017; Meng et al., 2019; Wang, 2018; Meira et al., 2022). These findings provide a strong biological basis for systematically evaluating its therapeutic potential against different human cancer cell lines.

Despite the growing number of studies investigating Physalis angulata L., the available evidence remains fragmented because different studies use various extraction methods, plant parts, extraction solvents, human cancer cell lines, and biological outcome measures. Moreover, the responsiveness of human cancer cell lines to herbal extracts may vary because of differences in genetic characteristics, receptor expression, and intracellular signaling pathways, making direct comparisons among studies difficult (Hanahan, 2022). To the best of our knowledge, no systematic review has specifically synthesized the available in vitro evidence regarding the antiproliferative activity, cytotoxic activity, anti-inflammatory activity, and molecular mechanisms of Physalis angulata L. across different human cancer cell lines.

In vitro studies represent an essential stage of preclinical research because they allow the early evaluation of cytotoxicity, selectivity, antiproliferative activity, anti-inflammatory activity, and molecular mechanisms before proceeding to in vivo experiments and clinical trials. Therefore, synthesizing evidence from multiple human cancer cell lines is important for identifying the spectrum of biological activity and determining which cell lines are most responsive to Physalis angulata extracts. Therefore, this study aims to systematically review the available in vitro evidence regarding the antiproliferative activity, cytotoxic activity, anti-inflammatory activity, molecular mechanisms, and overall effectiveness of Physalis angulata extracts against various human cancer cell lines. The systematic approach follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to minimize selection bias, improve methodological transparency, enhance reproducibility, and provide a more robust synthesis of evidence than conventional narrative reviews (Page et al., 2021). The findings of this systematic review are expected to provide a scientific basis for the development of Physalis angulata L. as a potential anticancer phytopharmaceutical, identify the most responsive human cancer cell lines, and guide future preclinical and translational studies.

2. METHOD

The study methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant studies were identified through searches in the PubMed and ScienceDirect databases, covering publications from October 2015 to October 2025. The search strategy in PubMed used the following keywords: ("Physalis angulata" OR "Physalis angulata L." OR physalin OR withanolide OR "steroidal lactone" OR "ground cherry" OR "ciplukan") AND (cancer OR tumor OR neoplasm OR carcinoma OR malignan OR oncogenic OR cytotoxic OR antiproliferative OR antineoplastic). In ScienceDirect, the search terms were limited due to word constraints and included: ("Physalis angulata L." OR physalin OR withanolide) AND (cancer OR carcinoma OR cytotoxic OR antiproliferative) AND (in vitro OR in vivo).

The inclusion criteria were as follows: (i) articles published in English, (ii) in vitro study design, (iii) interventions using Physalis angulata plant extracts as the primary material with compound isolation procedures, and (iv) studies involving human cancer cell cultures. The exclusion criteria included: (i) in vivo studies and review articles, (ii) studies that did not specify the source of the intervention material, and (iii) studies that did not perform compound isolation. The selected studies were analyzed based on: (i) country of origin, (ii) plant parts and compounds tested, (iii) comparator groups, (iv) extraction and isolation methods, (v) biological models, (vi) measured outcomes, and (vii) study findings. Outcomes were recorded based on the Inhibitory Concentration 50% (IC50), defined as the concentration of a compound required to inhibit 50% of cancer cell growth in vitro, expressed in μM.

3. RESULT AND DISCUSSION

Result

After literature screening using the PRISMA method, six studies met the inclusion criteria (Figure 1). All selected studies were in vitro, conducted outside a living organism using cell culture

models. The included studies focused on bioactive compounds derived from *Physalis angulata L.* Variations were observed in the plant parts used; two studies examined only the leaves and stems,

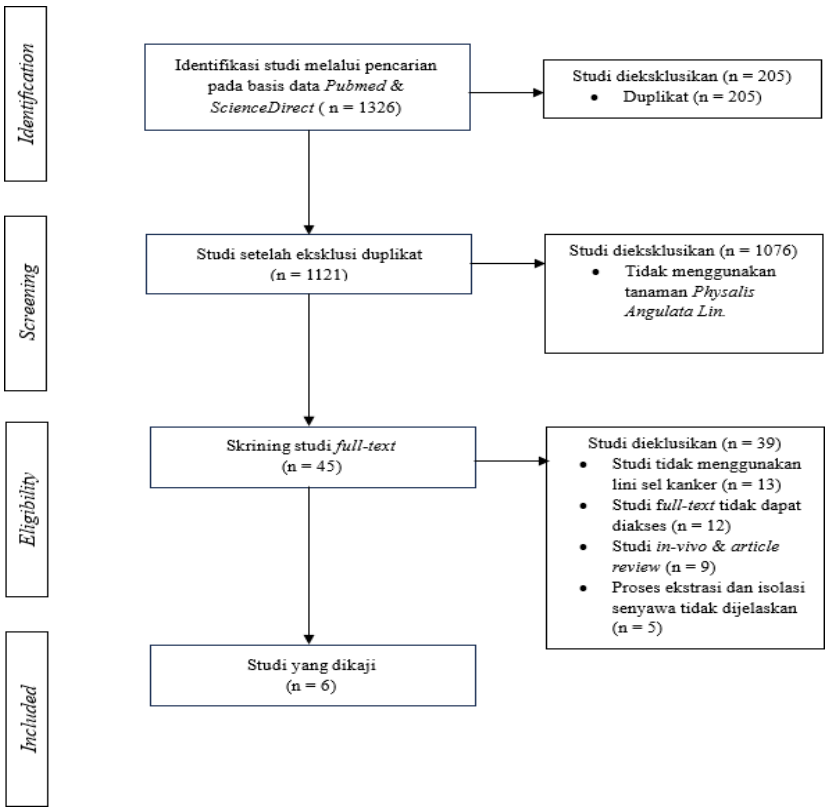

Figure 1. PRISMA flow-chart

Two studies used the stems, leaves, flowers, and fruits, while two others used the whole plant, including roots, stems, leaves, flowers, and fruits. All studies dried the plant materials prior to extraction and applied High-Performance Liquid Chromatography (HPLC) for compound analysis. After extraction, the therapeutic potential of the active compounds was evaluated across various human cancer cell lines. These included Non-Small Cell Lung Cancer (A549), multidrug-resistant Small Cell Lung Cancer (H69AR), cervical cancer (HeLa), leukemia (P388, HL-60), T lymphoblasts (MOLT-3), osteosarcoma (MG-63), hepatoma (HepG-2), human liver cancer (S102), cholangiocarcinoma (HuCCA-1), breast cancer (MDA-MB-231), hormone-dependent breast cancer (T47-D), prostate cancer (C4-2B, 22Rv1), kidney cancer (786-O, A-498, ACHN), and melanoma (A375-S2). In addition to anticancer activity, three studies assessed anti-inflammatory effects using RAW 264.7 macrophage cells, and one study evaluated apoptosis through Annexin V protein expression. The full characteristics of the included studies are presented in Table 1.

Overall, all six included studies consistently reported antiproliferative and cytotoxic activity of Physalis angulata L.-derived compounds against multiple human cancer cell lines. Three studies additionally demonstrated significant anti-inflammatory activity through inhibition of nitric oxide (NO) production in LPS-stimulated RAW264.7 macrophages. Withanolides, particularly physalins and physagulides, were the most frequently isolated bioactive compounds. Among the evaluated cancer models, prostate cancer (C4-2B and 22Rv1), renal carcinoma (ACHN and A498), multidrug-resistant small-cell lung cancer (H69AR), and triple-negative breast cancer (MDA-MB-231) appeared to be the most responsive, with several compounds exhibiting submicromolar IC_{50} values.

The isolation of active compounds from *Physalis angulata* began with extraction using polar to semi-polar solvents. Two studies used ethanol at concentrations of 75–95% to extract stems, leaves, or whole plants (Sun et al., 2016; Sun et al., 2017; Meng et al., 2019). Two other

studies used methanol (MeOH) as the primary solvent (Gao et al., 2017; Tuan Anh et al., 2020), while one study used a combination of hexane, dichloromethane, and methanol (Boonsombat et al., 2019). The extraction process involved maceration performed two to three times, followed by purification using chromatographic techniques. These included Column Chromatography (CC) with silica gel, Sephadex LH-20, and Octadecylsilane (ODS), with High-Performance Liquid Chromatography (HPLC) as the main method to obtain purified compounds. Some studies also applied Thin-Layer Chromatography (TLC) during the isolation process.

Most isolated compounds belonged to the withanolide and physalin groups, which are steroidal lactone derivatives commonly found in the Physalis genus. These compounds consistently demonstrated strong cytotoxic and antiproliferative activity against various human cancer cell lines. Across the six in vitro studies, these compounds showed considerable potential as natural anticancer agents, with IC_{50} values ranging from submicromolar to low micromolar levels. Sun et al. (2016) isolated 28 withanolide compounds from *P. Angulata* extracts. Compounds such as Physalin B (9), Physagulide J (17), Physagulin A (20), Physagulin B (21), Physagulin E (22), Physagulin I (25), and Physagulide I (27) demonstrated strong cytotoxic activity against multiple cancer cell lines, particularly prostate cancer (C4-2B, 22Rv1) and renal carcinoma (ACHN, A498), with IC_{50} values ranging from 0.18 to 2.43 μM. Several compounds, including Physagulide J (17), Physagulin A (20), Physagulin B (21), Physagulin I (25), and Physagulide I (27), also showed activity against melanoma cells, with IC_{50} values between 0.42 and 7.43 μM.

These findings are consistent with the study by Boonsombat et al. (2019), which reported strong cytotoxic effects of Physalin B (2) against H69AR cancer cells (IC50 3.25 μM), approximately 40-fold more potent, and against MDA-MB-231 breast cancer cells (IC50 0.82 μM), about 10-fold more potent than doxorubicin. In addition, Physalin F (4) also exhibited strong cytotoxic activity in the same cell lines, with IC50 values of 0.76 μM in both H69AR and MDA-MB-231 cells, corresponding to 48-fold and 3-fold greater potency than doxorubicin, respectively. However, in this study, several compounds, including Physalin D (3), Physalin G (5), and Physalin F (6), did not demonstrate significant cytotoxic activity.

This systematic review aimed to evaluate the therapeutic potential of *Physalis angulata* extracts against various human cancer cell lines. The findings indicate that withanolide compounds, particularly physalin and physagulide, exhibit consistent cytotoxic and anti-inflammatory activity across multiple cancer models. The low IC_{50} values highlight the strong potential of withanolide fractions from *P. Angulata* as natural anticancer candidates.

The anticancer activity of these compounds is primarily mediated through the induction of oxidative stress driven by increased Reactive Oxygen Species (ROS) and the activation of intrinsic apoptosis via the mitochondrial pathway. Elevated ROS levels disrupt mitochondrial function by altering the mitochondrial membrane potential. This disruption leads to the release of cytochrome c into the cytosol, followed by activation of caspase-9 and caspase-3, resulting in DNA fragmentation and programmed cell death. ROS also promotes apoptosis through activation of the JNK signaling pathway, which enhances pro-apoptotic factors. In addition, ROS activates the p38 pathway, leading to activation of the p53-Noxa axis, which increases pro-apoptotic proteins such as Bax and Bak, while reducing anti-apoptotic proteins like Bcl-2. The general mechanism of physalin action within the Mitogen-Activated Protein Kinase (MAPK) pathway is illustrated in Figure 2.

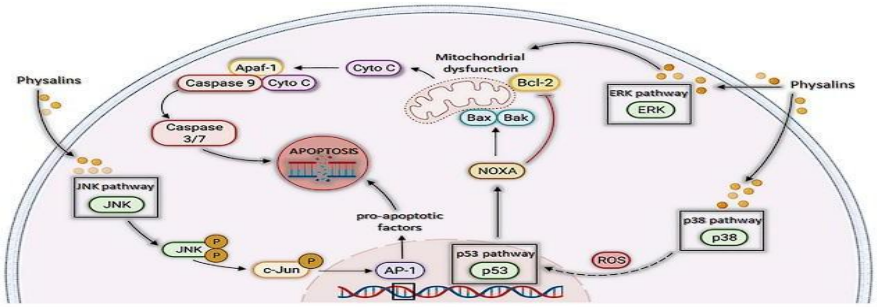

Figure 2. Mechanism of physalins in apoptosis induction (Meira et al., 2022)

Physalin A exerts anticancer effects through two main processes, apoptosis and autophagy. Increased ROS activates the p53-Noxa pathway and triggers pro-apoptotic signaling in cancer cells. In addition, activation of p38 associated with NF-κB induces a protective autophagic response (He et al., 2013). Physalin B promotes the upregulation of p53 and p21, leading to cell cycle arrest. This compound also reduces the phosphorylation of PI3K, Akt, and GSK-3β, indicating the involvement of the PI3K/Akt pathway in the regulation of cell death (Ma et al., 2015 & Wang et al., 2018).

No	Author (Year)	Country	Plant Part / Compounds	Control Group	Extraction / Isolation Method	Biological Model	Outcomes Measured	Study Findings
	Sun et al., 2016	China	Dried stems and leaves (9.5 kg); 16 new compounds (Physangulatins A–N, Withaphysalins Y–Z), 12 known analogs	Hydrocortisone (positive control)	75% ethanol (2x) → EtOAc → CC (silica gel, Sephadex LH-20, ODS) → TLC & HPLC	Prostate (C4-2B, 22Rv1); Renal (786-O, A-498, ACHN); Melanoma (A375-S2); RAW264.7	Cytotoxicity (MTT); NO inhibition (Griess)	Compounds 9,17,20–22,25,27 (IC50 0.18–2.43 μM); melanoma (0.42–7.43 μM); NO (1.36–5.56 μM)
	Sun et al., 2017	China	Dried stems and leaves (9.5 kg); 5 new compounds (Physalin V–IX), 11 known analogs	5-FU (positive control)	75% ethanol (2x) → EtOAc → CC → TLC & HPLC	Prostate; Renal; Melanoma; RAW264.7	Cytotoxicity; NO inhibition	Compounds 9,10 (IC50 0.24–3.17 μM); NO (0.32–4.03 μM)
	Gao et al., 2017	China	Dried stems, leaves, flowers, fruits (1 kg); 1 new compound (Physagulide P), 5 known analogs	Doxorubicin	DCM:MeOH (1:1) (3x) → CC → HPLC	MG-63; HepG-2; MDA-MB-231	Cytotoxicity	IC50 3.50, 4.22, 15.74 μM; compounds (2,4,6) 1.1–9.46 μM
	Meng et al., 2019	China	Dried stems, leaves, flowers, fruits (6.2 kg); 2 new compounds, 6 known analogs	Adriamycin	95% ethanol (3x) → DCM → CC → Sephadex → HPLC	A549; HeLa; p388	Cytotoxicity; Apoptosis (Annexin V)	IC50 11.36 μM, 21.75 μM, 8.03 μM; compounds 5,7 (1.91–7.85 μM); apoptosis up to 49.2%
	Boonsombat et al., 2019	Thailand	Dried whole plant (19 kg); 1 new compound (Physalin XI), 5 known analogs	Doxorubicin, etoposide	Hexane, DCM, MeOH (2x) → CC → Sephadex → HPLC	A549; HeLa; HL-60; MOLT-3; HuCCA-1; HepG2; MDA-MB-231; T47-D; S102; H69AR	Cytotoxicity (MTT, XTT)	Physalin XI inactive; compounds (2,4) IC50 0.76–3.25 μM
	Tuan Anh et al., 2020	Vietnam & Korea	Dried whole plant (2 kg); 1 new compound (Physalucoside A), 10 known analogs	Cardamonin; etoposide	MeOH (3x) → DCM → EtOAc → CC → Sephadex → HPLC	A549; HeLa; Panc-1; RAW264.7	Cytotoxicity; NO inhibition; iNOS & COX-2	NO IC50 <1 μM; Physalucoside A 2.69 μM; cytotoxic 0.68–1.03 μM

Discussion

Physalin F and Physagulide P exhibit similar mechanisms in intrinsic apoptosis. However, Physalin F also inhibits the phosphorylation of IκBα and prevents the nuclear translocation of p65/p50, thereby suppressing the expression of pro-survival genes such as XIAP and Survivin (Meira et al., 2022). Physagulide P also acts through activation of the JNK pathway and increases LC3-II levels and autophagosome formation, indicating a role of autophagy in cell death (He et al., 2013; Gao et al., 2017).

In addition to inducing cell death, several compounds in *P. Angulata* regulate cancer cell proliferation and survival by targeting key signaling pathways. Physalin A suppresses JAK phosphorylation and inhibits STAT3 translocation to the nucleus, leading to reduced expression of Bcl-2 and XIAP (Zhu et al., 2016). Physalin F promotes β-catenin degradation in the Wnt/β-catenin pathway, while Physalin H inhibits GLI-1 activity in the Hedgehog pathway (He et al., 2013; Meira et al., 2022; Chen et al., 2018) (Figure 3).

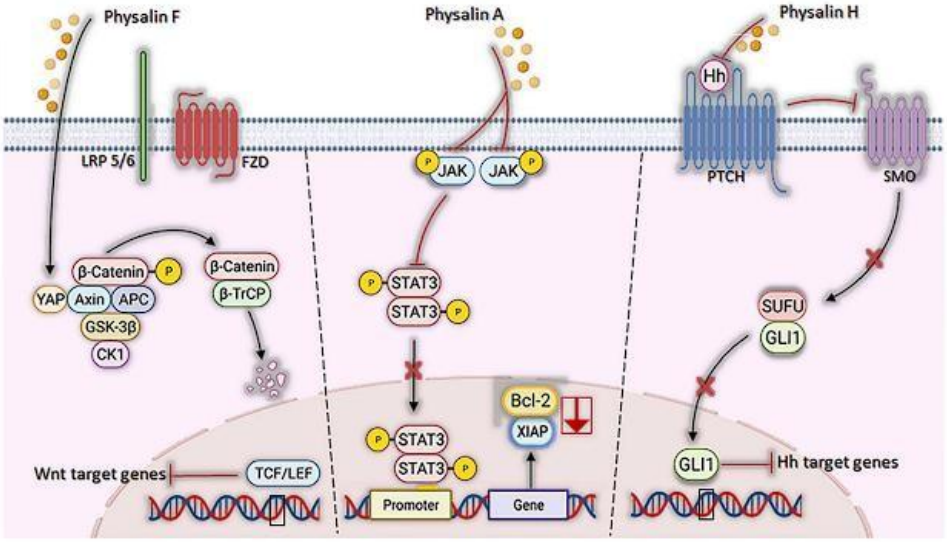

Figure 3. Mechanisms of physalins F, A, and H in disrupting the Wnt/β-catenin, JAK, and Hedgehog (Hh) signaling pathways (Meira et al., 2022)

In addition to apoptosis and autophagy, studies by Sun et al. (2016), Sun et al. (2017), and Tuananh et al. (2020) demonstrated significant anti-inflammatory effects in Lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophage cells. Physalin B and Physalin F consistently showed a significant reduction in Nitric Oxide (NO) levels in two studies. Other compounds, including Physalin H, isophysalin B, physangulatin I, physagulin A, B, H, I, and N, as well as physagulide I, also reduced NO levels, although these findings were limited to single studies.

NO serves as a marker of inflammation and is produced when macrophages are stimulated by inflammatory signals such as LPS. This response increases the activity of inducible Nitric Oxide Synthase (iNOS), which converts L-arginine into NO, and cyclooxygenase-2 (COX-2), which converts arachidonic acid into prostaglandin (PGE2). Elevated levels of NO and PGE2 promote inflammatory processes, including vasodilation and the release of other inflammatory mediators. Physalin reduces the activity of IκB Kinase (IKK), preventing the phosphorylation of inhibitor of kappa B (IκB). As a result, IκB remains in the cytoplasm bound to NF-κB, blocking its translocation into the nucleus. This leads to reduced production of pro-inflammatory cytokines and increased expression of the anti-inflammatory cytokine Interleukin-10 (IL-10) (**Figure 4**) (Hinz & Scheidereit, 2014; Meira et al., 2022).

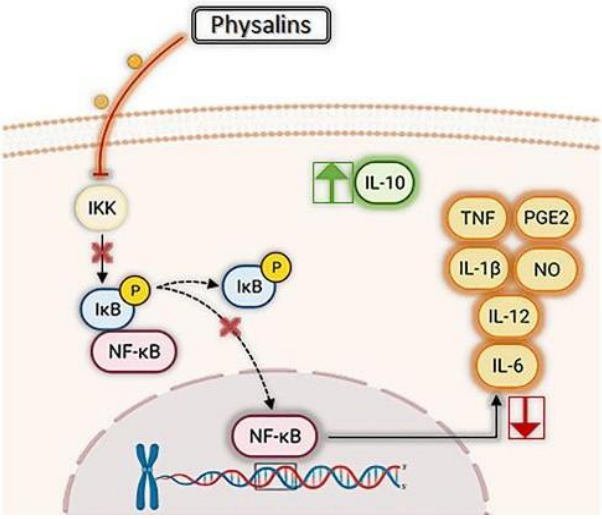

Figure 4. Anti-inflammatory effects of physalins (Meira et al., 2022)

This study has several limitations. All included studies were in vitro experiments using human cancer cell lines and LPS-induced RAW 264.7 macrophages, which limits direct clinical applicability. Further supporting studies are required before translation into clinical settings. In addition, no formal assessment of study quality or risk of bias was conducted. Variations in plant materials, extraction solvents, and cell models also limited quantitative comparison across studies. The overall quality of evidence remains limited because all included studies were preclinical in vitro experiments. Most studies originated from Asian countries, primarily China, and employed HPLC-based phytochemical isolation. Although the findings consistently demonstrated biological activity, the current evidence is insufficient to support clinical recommendations without further validation in animal models and human studies.

These findings provide direction for future research. In vivo and clinical studies are required to confirm safety and efficacy in humans. Further investigation is needed to clarify the molecular mechanisms of other physalin compounds and to develop effective delivery strategies that target cancer cells while minimizing toxicity to normal cells. This review supports the potential of *P. Angulata* as a natural anticancer agent with dual functions, targeting cancer cell viability and suppressing tumor-associated inflammation.

4. CONCLUSION

This systematic review demonstrates that extracts and active compounds from Physalis angulata L., particularly withanolide derivatives such as physalin, physagulide, and physangulatin, exhibit strong cytotoxic and antiproliferative activity against various human cancer cell lines. IC_{50} values fall within submicromolar to low micromolar ranges, indicating high potential as natural anticancer agents. Consistent mechanisms across studies include increased Reactive Oxygen Species (ROS) production, induction of apoptosis via the mitochondrial pathway, and inhibition of key signaling pathways, including MAPK, NF-κB, JAK/STAT3, Wnt/β-catenin, and Hedgehog. Anti-inflammatory activity also contributes through reduced expression of iNOS, COX-2, TNF-α, and IL-6, along with increased IL-10 expression.

5. REFERENCES

Alberts, B., Johnson, A., Lewis, J., Morgan, D., Raff, M., Roberts, K., and Walter, P. 2022. Molecular Biology of the Cell, 7th ed. New York: W. W. Norton & Company.

Bray, F. et al. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for
Clinicians, 68(6), 394–424.

Chen, C.C., Chen, Y.J., Tseng, C.H. and Chen, C.Y. 2018. Physalin F inhibits Wnt/β-catenin signaling by promoting β-catenin degradation in colorectal cancer cells. Biochemical Pharmacology, 152, 120–131.

Förstermann, U. and Sessa, W.C. 2012. Nitric oxide synthases: regulation and function. European Heart Journal, 33(7), 829–837.

Gao, C., Li, R., Zhou, M., Yang, Y., Kong, L. and Luo, J. 2018. Cytotoxic withanolides from Physalis angulata. Natural Product Research, 32(6), pp.676-681.

Han, H., Qiu, L., Wang, X., Qiu, F., Wong, Y. and Yao, X., 2011. Physalins A and B inhibit androgen-independent prostate cancer cell growth through activation of cell apoptosis and downregulation of androgen receptor expression. Biological and Pharmaceutical Bulletin, 34(10), pp.1584-1588.

Hasan, H., Aris, M., Pribadi, F. W., Ghozaly, M. R., Paturusi, A. A. E., Utami, Y. P., ... & Rita, R. S. (2024). Farmakognosi Dan Fitokimia: Dasar Pengobatan Herbal. Repositori Kakinaan.

He, W., Li, Y., Tang, X., Zhang, X. and Wang, Y. 2013. Physalin A induces apoptosis and autophagy via the ROS-mediated JNK and p38 pathways in human melanoma cells. Cancer Letters, 333(2), 275–285.

Hinz, M. and Scheidereit, C. 2014. The IκB kinase complex in NF-κB regulation and beyond. EMBO reports, 15(1), pp.46-61.

Jenča, A., Mills, D.K., Ghasemi, H., Saberian, E., Jenča, A., Karimi Forood, A.M., Petrášová, A., Jenčová, J., Jabbari Velisdeh, Z., Zare-Zardini, H. and Ebrahimifar, M. 2024. Herbal therapies for cancer treatment: a review of phytotherapeutic efficacy. Biologics: Targets and Therapy, pp.229-255.

Meira, C.S., Soares, J.W.C., Dos Reis, B.P.Z.C., Pacheco, L.V., Santos, I.P., Silva, D.K.C., de Lacerda, J.C., Daltro, S.R.T., Guimarães, E.T. and Soares, M.B.P. 2022. Therapeutic applications of physalins: powerful natural weapons. Frontiers in Pharmacology, 13, p.864714.

Ma, Y.M., Han, W., Li, J., Hu, L.H. and Zhou, Y.B. 2015. Physalin B not only inhibits the ubiquitin-proteasome pathway but also induces incomplete autophagic response in human colon cancer cells in vitro. Acta Pharmacologica Sinica, 36(4), pp.517-527.

Meng, Q., Fan, J., Liu, Z., Li, X., Zhang, F., Zhang, Y., Sun, Y., Li, L., Liu, X. and Hua, E. 2019. Cytotoxic withanolides from the whole herb of Physalis angulata L. Molecules, 24(8), p.1608.

Newman, D.J. and Cragg, G.M. 2020. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. Journal of Natural Products, 83(3), 770–803.

Nurulita, D. 2025. Potensi tanaman ciplukan (Physalis angulata L.) sebagai agen antikanker. Action Research Literate. 9(6):1079-1086

Sulaiman, C., George, B.P., Balachandran, I. and Abrahamse, H. 2025. Cancer and Traditional Medicine: An Integrative Approach. Pharmaceuticals, 18(5), p.644.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F. 2021. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 71(3), 209–249.

Sun, C.P., Qiu, C.Y., Yuan, T., Nie, X.F., Sun, H.X., Zhang, Q., Li, H.X., Ding, L.Q., Zhao, F., Chen, L.X. and Qiu, F. 2016. Antiproliferative and anti-inflammatory withanolides from Physalis angulata. Journal of natural products, 79(6), pp.1586-1597.

Sun, C.P., Qiu, C.Y., Zhao, F., Kang, N., Chen, L.X. and Qiu, F. 2017. Physalins V-IX, 16, 24-cyclo-13, 14-seco withanolides from Physalis angulata and their antiproliferative and anti-inflammatory activities. Scientific reports, 7(1), p.4057.

Tuan Anh, H.L., Le Ba, V., Do, T.T., Phan, V.K., Pham Thi, H.Y., Bach, L.G., Tran, M.H., Tran Thi, P.A. and Kim, Y.H. 2021. Bioactive compounds from Physalis angulata and their anti-inflammatory and cytotoxic activities. Journal of Asian Natural Products Research, 23(8), pp.809-817.

Wang, A., Wang, S., Zhou, F., Li, P., Wang, Y., Gan, L. and Lin, L. 2018. Physalin B induces cell cycle arrest and triggers apoptosis in breast cancer cells through modulating p53-dependent apoptotic pathway. Biomedicine & Pharmacotherapy, 101, pp.334-341.

Wu, S.Y., Leu, Y.L., Chang, Y.L., Wu, T.S., Kuo, P.C., Liao, Y.R., Teng, C.M. and Pan, S.L. 2012. Physalin F induces cell apoptosis in human renal carcinoma cells by targeting NF-kappaB and generating reactive oxygen species. PloS one, 7(7), p.e40727.

Zhu, F., Dai, C., Fu, Y., Loo, J.F., Xia, D., Gao, S.P., Ma, Z. and Chen, Z. 2016. Physalin A exerts anti-tumor activity in non-small cell lung cancer cell lines by suppressing JAK/STAT3 signaling. Oncotarget, 7(8), p.9462.