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Review Article

# AYURVEDIC HERBS TARGETING CELL CYCLE CHECKPOINTS IN CANCER

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## ABSTRACT

Malfunctioning cyclin-dependent kinases, defects in the DNA damage response, and aberrations in mitotic checkpoints maintain unregulated proliferation, a hallmark of cancer. Ayurvedic medicinal plants contain various chemical constituents that may act on these pathways. The biological impact of altered cell cycle status varies across experimental models. This critical narrative review evaluates studies published from 2020 to 2025 on the potential impact of curcumin from Curcuma longa, withaferin A from Withania somnifera, nimbolide from Azadirachta indica, andrographolide from Andrographis paniculata, and preparations from Ocimum tenuiflorum, Tinospora cordifolia, Boswellia serrata, and Phyllanthus emblica on cell cycle and checkpoint regulation. Studies have reported effects of curcumin on S-phase, withaferin A and andrographolide on G2/M phase arrest and nimbolide on DNA damage or ER stress. Protein expression changes or cytotoxicity, and in silico docking do not indicate checkpoint engagement. Genetic validation of cell-cycle checkpoint regulators for these natural products remains limited. Most of the evidence is from studies using cancer cell lines and/or animals. Other limitations, such as compositional heterogeneity, extract exposure and selectivity, and reproducibility, also apply to these studies. Given the current preclinical evidence, some Ayurvedic compounds may be pharmacologically useful for cancer, and warrant further study in the context of efficacy, safety and targeted cancer therapy.

## INTRODUCTION

Key events in malignant cell division include repeated division despite anti-proliferative signals, failure to arrest or undergo cell death, and adaptation to genomic instability. Progression through the cell cycle is regulated by sequential activities of cyclin-CDK complexes. Molecular surveillance systems respond to replication stress/DNA damage. Alterations in RB/E2F, CDKN1A, and CDK regulatory networks confer clinical impact. This is evident from the therapeutic use of CDK4/6 inhibitors and DNA damage response modulators. Recognising these successes provides a framework for assessing other candidate molecules.[2-5]

Ayers interprets Ayurvedic plants in terms of crude extractions rather than pure chemical entities.

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Although numerous reports of antiproliferative activity exist, evidence of engagement of cell cycle checkpoints remains limited. Here, we document the basis for this distinction and stress the importance of experimental context, especially against the indiscriminate labelling of investigational materials as “anticancer” agents.[18-23, 27-37, 39-43]

## MATERIALS AND METHODS

This is a critical narrative synthesis rather than a registered systematic review or meta-analysis. We identified studies indexed in PubMed from 2020 to 2025 by searching selected publishers and evaluated them by title and abstract for molecular relevance. Mechanistic claims were drawn from primary literature and focused reviews. No claim of exhaustive searches of multiple databases, or quantification of pooled effects, is made. No formal risk-of-bias assessment is made.

Papers with retraction or reliability concerns were not used to substantiate experimental conclusions. The numbered bibliography contains supported sources instead of unsupported additions to

meet a quota. We verified the supporting evidence for this manuscript and did not add unverified sources.

## Cell-Cycle Checkpoints and Malignant Proliferation

### G1/S restriction point and replication licensing

MRF-activated Cyclin D-CDK4/6 activity allows the phosphorylation of RB to license E2F-mediated transcription of S phase programs. Cyclin E-CDK2 re-enforces commitment to the DNA replication program. Simultaneously, p53 activation transcriptionally upregulates CDKN1A (p21), mediating G1 arrest. Reported alterations in these proteins following phytochemical exposure may reflect a G1/S phase phenotype, but evidence for protein abundance does not prove direct enzymatic inhibition. A mechanism of action requires phase-specific distribution and target activity, and rescue experiments [1-8,12,17].

### Intra-S and G2/M responses

Replication stress forms single-stranded DNA (ssDNA) structures that stimulate the ATR pathway. Upon ATR signalling, CHK1 maintains fork stability and prevents inappropriate origin firing. In the absence of ssDNA structures, ATM-CHK2 pathway is primarily activated by dsB. WEE1, along with CDC25 phosphatases, regulates CDK1 to control mitotic entry. Tumors deficient in G1 controls may become overly reliant on G2 controls. Agents shifting cells from G2 to M phase may do so through various mechanisms, including DNA damage, spindle poisons, and other toxic stresses [3-5].

### Mitosis and spindle checkpoint

Once the spindle assembly checkpoint is satisfied, chromosomes separate during anaphase. Disruption of the checkpoint leads to chromosomal imbalance and is lethal. The loss of mitotic surveillance, demonstrated in breast cancer models, may be amenable to therapeutic targeting. Although treatment with a mitotic inhibitor may produce an apparent G2/M peak, this may also reflect a G2 arrest; mitotic markers may help distinguish the two [1,6].

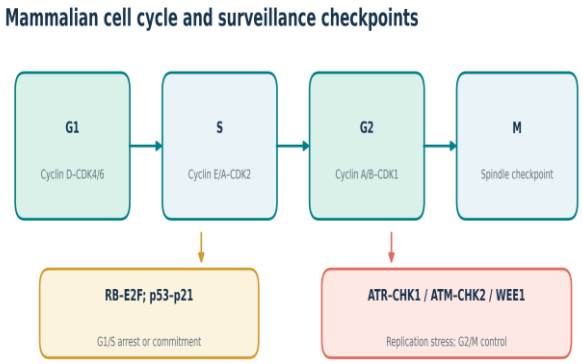



**Fig. 1. Core mammalian cell-cycle transitions and checkpoint-associated regulatory modules. Original schematic; not a quantitative data figure**

## Botanical Compounds and Checkpoint-Associated Findings

### *Curcuma longa*: Curcumin and related chemical derivatives

Curcumin is widely studied but shows model-dependent phase effects. An investigation on colon cancer revealed that curcumin induced S-phase arrest and apoptosis and is related to RB/E2F/p53. However, a neuroblastoma model showed that curcumin caused G2/M phase arrest and was associated with reactive oxygen species (ROS) and p53. Co-treatment of breast cancer cells with melphalan and doxorubicin in the presence of curcumin induced cell-cycle arrest and cell death. However, it is not appropriate to assign the entire effect to curcumin in these combinations. A curcumin/piperlongumine hybrid, and NC2603, a synthetic derivative of curcumin, should not be considered equivalent to dietary curcumin. Studies on NC2603 have shown regulation of CDKN1A, indicating the need for detailed pharmacological studies of the compounds.[12,13,14,15,16,17]

### Withania somnifera: Withaferin A

Researchers are studying withaferin A for its potential to treat various cancers. In a model of KLE endometrial carcinoma, researchers observed that withaferin A induced G2/M arrest due to the inhibition of TGF-β/SMAD signaling. In colorectal cancer, withaferin A induced apoptosis and autophagy and decreased β-catenin expression. It was shown to block c-Myc and induce ROS in a breast cancer model. These studies have a strong mechanistic foundation, but do not demonstrate (directly) that withaferin A binds to CDKs. With advances in computational biology, we can expect more detail on drug action. [18,19,20, 21,22, 23,24,25,50]

Formulation studies explored liposomal withaferin A to overcome delivery limitations. More recently, studies have shown withaferin A's potential in gastric and ovarian cancer models. Withaferin A's mechanisms of action include inhibiting AKT, NF-κB, STAT3, and survivin, suggesting it does not always need to act at the cell-cycle level to exert its anticancer effects.

Reports suggest that the strongest inference is that withaferin A perturbs multiple proliferation-related pathways, not that it targets a single universal checkpoint.[26,49]

### *Azadirachta indica*: Nimbolide

Researchers have also examined nimbolide for its effects on survival pathways, reactive oxygen species, endoplasmic reticulum stress, and DNA damage. One study reported that ROS-mediated endoplasmic reticulum stress and DNA damage occurred in non-small-cell lung cancer cells. In a separate report, oral squamous cell carcinoma cells underwent apoptosis associated with endoplasmic

reticulum stress. While these results may affect cell-cycle checkpoints, the cited studies do not indicate that nimbolide inhibits ATM, ATR, CDK1, or CDK4/6. More rigorous molecular studies are needed to elucidate these agents' selectivity.[27,28,29]

### Andrographis paniculata: Andrographolide

Andrographolide is more checkpoint-associated. HCT-116 colon cancer cells underwent G2/M arrest, with reduced Cyclin B1/CDK1 mRNA levels and modulation of the Hedgehog pathway. DBTRG-05MG glioblastoma cells underwent G2/M arrest and apoptosis with modifications in ERK1/2, c-Myc, and p53. A proteomic approach identified PDCD2 as a candidate interacting protein involved in nuclear import of CDK mRNA. Although docking studies formed the basis of the target hypothesis, strong target validation is essential. Modified andrographolide induced changes to the cell cycle in breast cancer. Colorectal cancer-based studies evaluated andrographolide for immunostimulation, tumour cell cycle, and ferroptosis.[9,10,11,30,31,32,33]

### Other Ayurvedic Plants: Strength of Specific Evidence

Tinospora cordifolia preparations have been associated with apoptosis, epithelial-mesenchymal transition, and other antitumor effects in oral cancers. Studies have shown it induces apoptosis in lung carcinogenesis.

Unlike Tinospora-derived small molecules, the effects of plant-assisted ZnO NPs may largely reflect the inorganic component. A 2025 study examining breast cells also tested a specific formulation, which may not extrapolate to other *Guduchi* preparations. Reviews list potential constituents, but checkpoint-specific validated targets are lacking. Safety is of particular importance as a recent multicenter case series reported acute liver injury associated with the use of Tinospora products. While related studies describe both attribution and species identification, recently published studies describe liver injury associated with the use of Tinospora products.[34,35,36,37,38,39,40]

Similar maturity in clinical research checkpoint interventions is expected for Ocimum tenuiflorum and Boswellia serrata. Phytochemical analyses for Ocimum tenuiflorum are more advanced, and an up-to-date botanical review may serve as a starting point for research; however, it does not justify its use in cancer treatment. For Boswellia serrata, Amin et al. posit that acetyl-11-keto-β-boswellic acid inhibits RAB7B and autophagy in oral squamous cell carcinoma. While the reviewers state That Acetyl-11-Keto-B-Boswellic Acid may act as a cyclin-dependent kinase (CDK) inhibitor, no clinical data support this claim. Phytochemical analysis of Phyllanthus emblica supports chemoprevention and provides a basis for future patient-level oncology studies.[41,42,43,44]

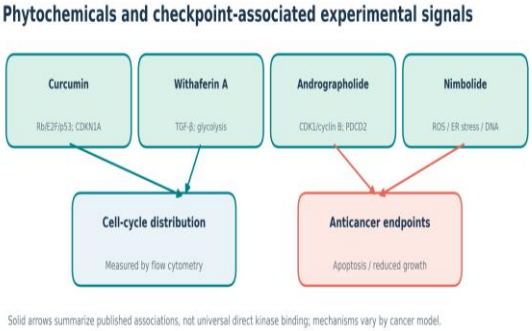



**Fig. 2. Selected plant-derived compounds and the experimental pathways associated with their anticancer phenotypes. Associations are context-dependent and do not establish universal direct binding**

### Comparative Mechanistic Interpretation

Investigations that detect a coherent causal chain from purified compound exposure to target modulation, cytometric phase distribution, checkpoint control, proliferation, and rescue are strongest for interpretation. Literature examples of curcumin and andrographolide support S-phase and G2/M phenotypes, respectively. Andrographolide studies report target modulation of Cyclin B1/CDK1 and an interaction with PDCD2. Withaferin A studies extend to SMAD, β-catenin, metabolism and epigenetics. Nimbolide studies report support for stress-associated apoptosis and genotoxicity. Anticancer cell death can occur without a primary checkpoint target. Temporary arrest can occur without cytotoxicity.[9,10,11,12,13,18,19,27,29] Cancer genotype modifies response. Loss of TP53 and constitutively active Cyclin D contribute to replication stress and influence whether the cell arrests, senesces, repairs, or undergoes apoptosis. An experimental phenotype in neuroblastoma cannot be assumed to reproduce in other cancers. Likewise, the absence of p21 does not establish causality with regard to P53, RB, or other signalling components. Mechanistic inference would benefit from protein inhibitors, orthogonal live-cell imaging, cellular target-engagement assays, and RNAi or CRISPR rescues.[1,2,3,8,12,13,17]

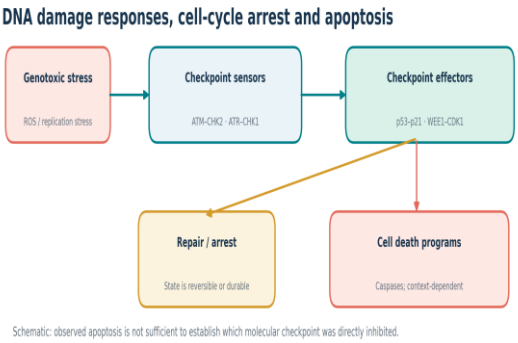



**Fig. 3. Biological relationships connecting DNA damage responses with arrest and cell-death programs.**

**Schematic relationships are not evidence that a particular herb directly inhibits each indicated protein**

**Computational Modeling, Drug Delivery and Clinical Translation**

Network pharmacology and docking studies predict binding sites and signaling pathways. However, these methods do not prove site targeting. For example, withaferin A is reported to target cancer through interaction networks. However, binding, target occupancy, and cellular studies at dose-relevant concentrations, along with genetic studies, are needed to confirm these interactions. Pharmacologic identity is critical. The phytochemical, plant extract, curcumin analogue, and nanoparticle preparation have different chemical profiles. Concentrations must be analysed to distinguish the chemical differences among these preparations and their potential impact on cellular activity. Comparing only nominal concentrations may be misleading.[21,26,31,47]

Limitations on translation may be due to a compound's chemical instability, metabolism, cellular activity, a compound's reactivity with off-target biomolecules and poor aqueous solubility, to name a few. Improving bioavailability may increase exposure, but it does not guarantee benefit. Studies focused on nanocurcumin and andrographolide solid dispersions have improved formulation. Outcomes from these studies remain primarily preclinical. True progress may come through authenticated plant material, improved extraction and chemistry, validated assays, and improved pharmacokinetics to support cell selectivity and toxicology across organ systems. [26,31,45,46,47]

Mechanistic emphasis needs counterweight from clinical evidence. A systematic review of randomised trials of adjunctive curcumin showed heterogeneous results; most studies were judged to be at moderate-to-high risk of bias, and no firm conclusions could be drawn about curcumin's efficacy in cancer treatment. A clinical trial appraisal highlighted design and bioavailability limitations. The clinical studies reviewed focused on specific formulations, bioavailability, and endpoints, rather than validated therapeutic inhibition of cell-cycle checkpoints. The compounds reviewed here should not replace surgery, radiotherapy, or other oncologic interventions.[45,46]

**Safety and botanical origin are unrelated.**

Herbal product constituents vary considerably and can interact with medicinal products that have a narrow therapeutic index. The literature on Tinospora and liver injury illustrates the need for species validation, product authentication, careful causality assessment, and ongoing pharmacovigilance. Even tumour cell line-restricted compounds warrant examination of normal cell proliferation, the immune system, and hepatic tissue. Controlled, combination clinical experiments should address antagonism and the clinical plausibility of achievable concentrations before synergistic claims can extend beyond the laboratory.[15,34,38,39,40]

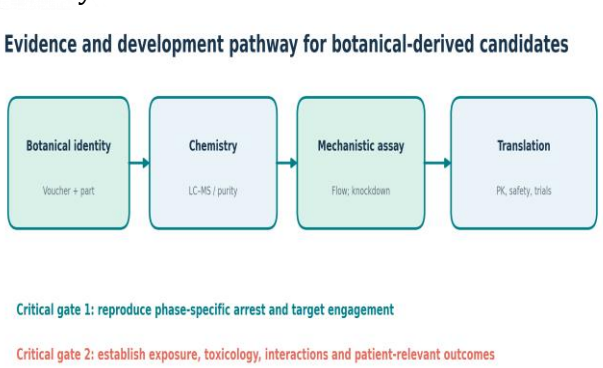



**Fig. 4. Translational development gates for botanically derived anticancer leads, from authentication and molecular validation to clinical evaluation**

**Table 1: Representative botanicals, material identity and reported anticancer endpoints**

| Plant and customary name | Source material / constituent | Cancer model | Reported phenotype | Evidence / reference |
|---|---|---|---|---|
| *Withania somnifera* / *Ashwagandha* | Withaferin A | KLE endometrial; breast; colorectal | G2/M or sub-G1 enrichment in model-specific studies | Cell / molecular [18–25] |
| *Curcuma longa* / Turmeric | Curcumin | Colon; neuroblastoma; breast | S-phase or G2/M; apoptosis; combination effects | Cell / molecular [12–17] |
| *Azadirachta indica* / *Neem* | Nimbolide | Lung; oral squamous | DNA damage or ER-stress-associated apoptosis | Cell / molecular [27–29] |
| *Andrographis paniculata* / *Kalmegh* | Andrographolide | HCT-116; DBTRG-05MG | G2/M; CDK1/cyclin B markers | Cell / proteomic [9–11] |

| | | | | |
|---|---|---|---|---|
| *Tinospora cordifolia* / *Guduchi* | Mixed extract / arabinogalactan | Oral; lung; breast models | Apoptosis; anti-EMT; other anticancer endpoints | Preclinical [34,35,37] |
| *Ocimum tenuiflorum* / *Tulsi* | Diverse plant constituents | Phytochemical literature | Checkpoint-specific inference is limited | Review [41] |
| *Boswellia serrata* / *Shallaki* | AKBA from resin | Oral squamous carcinoma | Growth inhibition; autophagy | Cell study [42] |
| *Phyllanthus emblica* / *Amla* | Fruit extract / polyphenols | Colon and liver rodent model | Chemopreventive endpoints | Animal / review [43,44] |

**Table 2: Selected checkpoint-associated molecular observations and interpretation**

| Agent | Study system | Observed molecular or phase-level finding | Interpretation limit | Source |
|---|---|---|---|---|
| Curcumin | Colon cancer model | S-phase response; RB/E2F/p53-related effects | Not proof of direct CDK inhibition | [12] |
| Curcumin | SK-N-SH neuroblastoma | G2/M accumulation; ROS/p53-associated effect | Cell-line specificity | [13] |
| NC2603 | MCF-7 | CDKN1A upregulation with cell-cycle arrest | Synthetic analog, not crude turmeric | [17] |
| Withaferin A | KLE endometrial | G2/M accumulation; TGF-β/SMAD association | Target causality not universal | [18] |
| Andrographolide | HCT-116 colorectal | Cyclin B1/CDK1 downregulation with G2/M arrest | Multiple Hedgehog-linked changes | [9] |
| Andrographolide | DBTRG-05MG glioblastoma | G2/M arrest; ERK/c-Myc/p53 association | In-vitro endpoint | [10] |
| Andrographolide | Tumor-cell proteome screening | Candidate PDCD2 binding; altered CDK mRNA export | Target requires replication | [11] |
| Nimbolide | Non-small-cell lung cancer | ROS, ER stress, DNA damage responses | Checkpoint phase not established | [27] |
| AKBA | Oral squamous carcinoma | RAB7B-linked autophagic effects | Not demonstrated kinase binding | [42] |

**Table 3: Evidence maturity and priorities for translational validation**

| Category | Existing evidence | Principal uncertainty | Priority |
|---|---|---|---|
| Curcumin | Multiple cell studies and clinical systematic reviews [12–17,45–47] | Bioavailability; inconsistent patient endpoints | Pharmacokinetics and rigorous RCTs |
| Withaferin A | Cell, formulation and xenograft signals [18–26,49] | Multitarget effects and achievable exposure | Target-engagement and safety |
| Andrographolide | Checkpoint, candidate target, delivery [9–11,30–33] | Cancer specificity and causal target pathway | Genetic rescue; repeatable assays |
| Nimbolide | Stress signaling and preclinical studies [27–29] | Direct checkpoint target unclear | Phase-resolved functional studies |
| Guduchi products | Heterogeneous preparations; safety reports [34–40,48] | Species identity, extract composition, hepatotoxicity | Authentication and toxicology |
| Other botanicals | Model-specific or supporting studies [41–44] | Scarce checkpoint-selective proof | Purified compounds and validated assays |

## Research Gaps and Future Perspectives

Five main points can be drawn from this evidence. First, when defining constituents, compare mechanisms. To support chemical characterisation, report botanical vouchers, plant parts, extraction solvents, measured constituents, and purity and batch variation. Second, for mechanistic comparison, use time-course and multiparameter cytometry to distinguish G1 arrest from replication delay and confirm G2 arrest and mitotic accumulation. Third, for kinases, perform both biochemical assays and target-occupancy measurements. Along with these studies, one should also perform knockdowns, CRISPR perturbations, and/or rescue studies. Alone, a change in abundance of a signalling protein is not sufficient to support a study. Fourth, one should assess metabolite activity, normal-cell toxicity, and tissue exposure. Fifth, based on reproducible preclinical data, determine whether clinical evaluation is warranted. A simple analysis of cell line cytotoxicity should not determine whether clinical evaluation is warranted.[1,3,4,11,17,27,39]

Incorporating omics sciences into biomedical research promises to improve the identification of disease biomarkers and therapeutic targets. Integrated Omics analyses may also provide clues about context-specific mechanisms underlying pathophysiology. In the absence of intervention studies, however, pathway enrichment analyses should be regarded as hypothesis-generating analyses. Although molecular docking predicts binding and offers structural support, it provides little evidence of clinical efficacy. Comparative research should evaluate checkpoint dependence in TP53/RB-deficient isogenic systems, report positive controls, exposure controls, predefined endpoints, and both absolute and relative cell counts. Cross-study synthesis would benefit from standardised data templates that distinguish extracts, pure compounds, and biotech derivatives. [20-24, 47-48]

## CONCLUSION

A number of Ayurvedic herbal products and their phytochemical constituents have been shown to modify the cell cycle, and when studied in context of certain experimental models, influence the distribution of cells in various phases of the cell cycle. Curcumin, withaferin A, and andrographolide have preclinical data supporting an influence on cell-cycle checkpoints. Likewise, nimbolide and other botanical preparations have endpoints that support broad anti-stress, anti-survival and chemoprevention roles.

Current data do not warrant description of these phytochemicals as established or selective cyclin-dependent kinase (CDK) or checkpoint inhibitors. Several gaps must be closed, including mechanistic validation, exposure and toxicology, before prospective animal and clinical studies can be designed and conducted. Pharmacological hypotheses can be generated from traditional use; it does not provide evidence for the oncological role.

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