# The Role of Phytocompounds in Disrupting Glioblastoma Pathways: A Cytotoxic and Enrichment Analysis

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**Abstract**: Glioblastoma (GB) is a highly aggressive brain tumor with limited treatment options. This current study assessed the cytotoxicity of six phytocompounds—colchicine, piperine, quercetin, theobromine, reserpine, and cineole—on LN229 and U-87 MGGB cell lines using MTT assay. Colchicine demonstrated potent cytotoxicity through microtubule disruption and oxidative stress modulation, while quercetin exhibited broad-spectrum activity, including apoptosis induction and chemosensitization. Reserpine selectively targeted GPCRs, reducing cell invasiveness and angiogenesis. Theobromine, cineole, and piperine showed limited direct cytotoxicity but displayed unique interaction profiles suggesting complementary therapeutic roles. Enrichment analysis highlighted pathways critical to GB, such as ROS metabolism and MAPK signaling. These findings underscore the potential of phytocompounds as standalone or combinatorial therapies for glioblastoma, warranting further in vivo and mechanistic studies.Colchicine, reserpine, and quercetin show promise as glioblastoma treatments due to their complementary mechanisms of action, warranting further in vivo studies and mechanistic exploration to confirm their clinical potential.

**Keywords**: Colchicine, Cytotoxicity, Phytocompounds, Piperine, Quercetin, Target prediction

## Introduction

Glioblastoma (GB) is the most aggressive and lethal primary brain tumor, characterized by rapid proliferation, invasive growth, and resistance to conventional therapies [1]. Despite advances in surgical resection, radiotherapy, and chemotherapy, the prognosis for GB patients remains dismal, with a median survival of only 12–15 months [2]. The complexity of GB lies in its highly heterogeneous molecular and cellular composition, which fosters resistance to treatment and recurrence [3]. Consequently, there is a pressing need to explore novel therapeutic strategies, including the use of natural phytocompounds, which offer multitargeted actions and minimal side effects.

Phytocompounds, derived from medicinal plants, have gained attention for their diverse pharmacological properties, including anti-inflammatory, antioxidant, and anticancer effects [4]. In this study, we have focused on six phytocompounds-colchicine, piperine, reserpine, theobromine, quercetin, and cineole, each with unique molecular mechanisms that may hold promise in combating glioblastoma. These compounds exhibit significant bioactivities, such as modulation of cell signaling pathways, inhibition of cell proliferation, induction of apoptosis, and chemosensitization, making them attractive candidates for cancer therapy.

Colchicine, a well-known microtubule-disrupting agent, has been extensively studied for its antiproliferative effects on cancer cells, including its ability to induce cell cycle arrest and apoptosis [5]. Piperine, a bioactive alkaloid from black pepper, has shown potential as an anti-inflammatory and pro-apoptotic agent, with documented roles in sensitizing cancer cells to chemotherapy [6]. Quercetin, a flavonoid abundant in fruits and vegetables, is widely recognized for its antioxidant and anti-inflammatory properties, as well as its ability to enhance the efficacy of conventional cancer treatments [7]. Reserpine, theobromine, and cineole, although less explored in glioblastoma have exhibited promising bioactivities such as modulation of ion channels, oxidative stress regulation, and interference with protein-protein interactions, which may contribute to their anticancer potential [8-10].

To unravel the therapeutic relevance of chosen phytocompounds (colchicine, piperine, reserpine, theobromine, quercetin, and cineole) in glioblastoma, we investigated their cytotoxic effects on GB cell lines LN229 and U-87 MG, alongside a detailed analysis of their molecular targets. Using a combination of cytotoxicity assays, computational tools, and protein interaction analyses, we explored the potential mechanisms underlying their effects. This study provides a comprehensive evaluation of these phytocompounds as potential candidates for glioblastoma therapy, paving the way for further research into their combinatorial and standalone applications in the clinical setting.

This research aims to bridge the gap in understanding the molecular actions of these phytocompounds and their implications in glioblastoma treatment, contributing to the growing field of plant-derived cancer therapeutics.

## Materials and Methods

### Cells and Reagents

The LN229 and U-87 MG glioblastoma cell lines were acquired from the National Centre for Cell Science (NCCS), Pune, India. The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and antibiotics (penicillin, streptomycin, and gentamycin) under standard incubation conditions of 5% $CO_2$ at 37°C.

### Cytotoxicity Evaluation

The cytotoxic effects of the phytocompounds on LN229 and U-87 MG cells were determined using the MTT assay, as outlined in a previous study. A total of $1 \times 10^5$ cells/mL were seeded in 96-well plates and treated with test compounds at concentrations ranging from 3.1 to 50 µM. Following 24 hours of treatment, 5 mg/mL MTT solution was added, and the plates were incubated for 4 hours at 37°C in 5% $CO_2$. The media was then removed, and 200 µL of DMSO was added to dissolve the formazan crystals [11]. Optical density (OD) was measured at 570 nm, and cell viability was calculated using the formula:

$$\text{Viability of cells (\%)} = \frac{\text{Treated cells} - \text{blank}}{\text{control cells} - \text{blank}} \text{ X } 100$$

Statistical Analysis

One-way ANOVA followed by Tukey's Honestly Significant Difference (HSD) post hoc test was performed for statistical comparisons. Analyses were conducted to compare control groups and single-compound treatments. Differences were deemed statistically significant for p-values below 0.05 or 0.01.

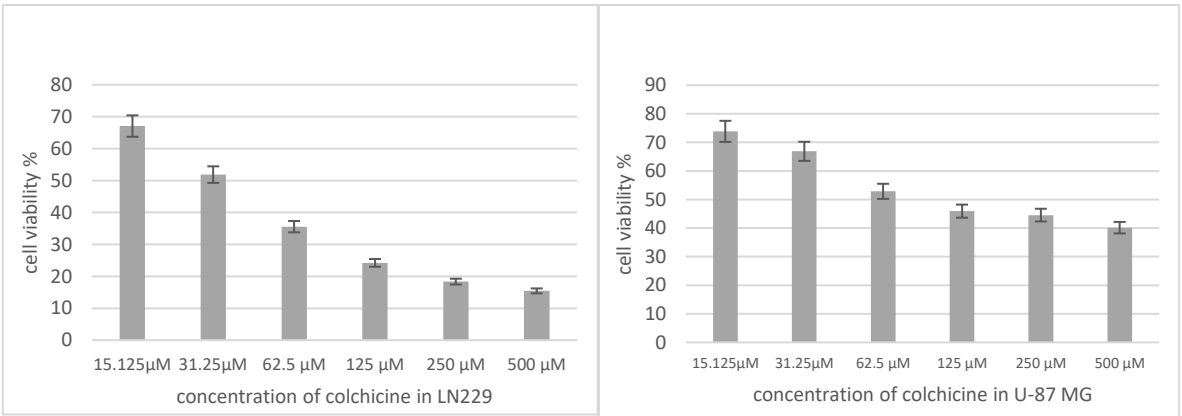
Swiss Target Prediction

The Swiss Target Prediction tool was used to identify probable protein targets of the phytocompounds. The chemical structures of the compounds were uploaded, and the tool analyzed their similarity to known bioactive molecules to predict potential therapeutic targets [12].

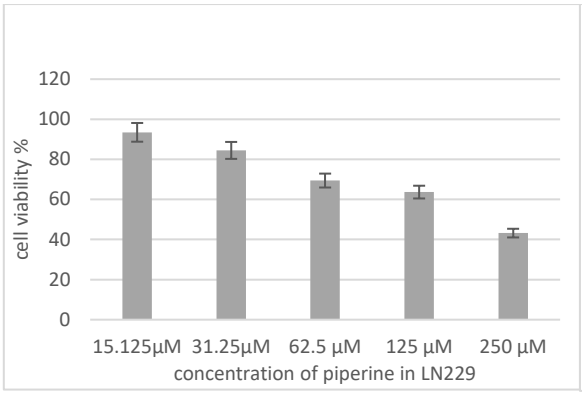
Web Gestalt Analysis

The Web Gestalt tool was utilized to explore the functional pathways associated with the identified protein targets. Gene Ontology (GO) analysis was conducted to assess biological processes, cellular components, and molecular functions, while KEGG pathway enrichment was used to identify relevant molecular pathways. These analyses provided insights into the cellular mechanisms modulated by the phytocompounds [12].

## Result and Discussion




(A) (B)


120
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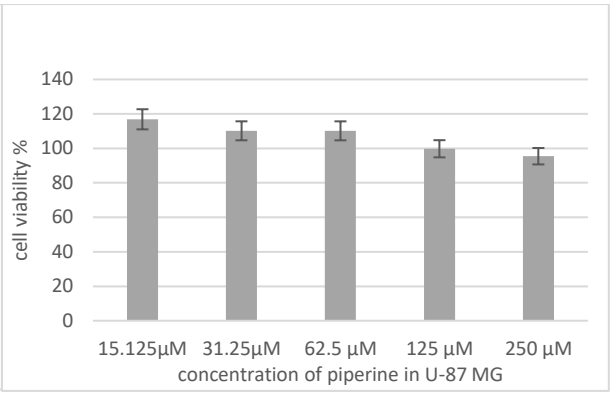
cell viability %
15.125µM 31.25µM 62.5 µM 125 µM 250 µM
concentration of piperine in LN229

(C)


140
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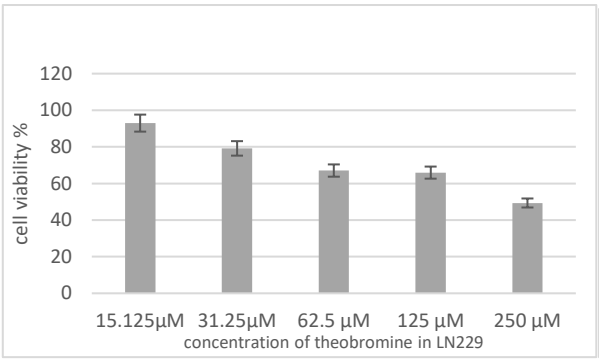
cell viability %
15.125µM 31.25µM 62.5 µM 125 µM 250 µM
concentration of piperine in U-87 MG

(D)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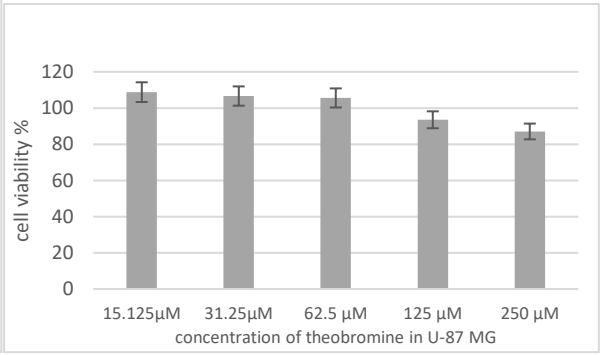
concentration of theobromine in LN229

(E)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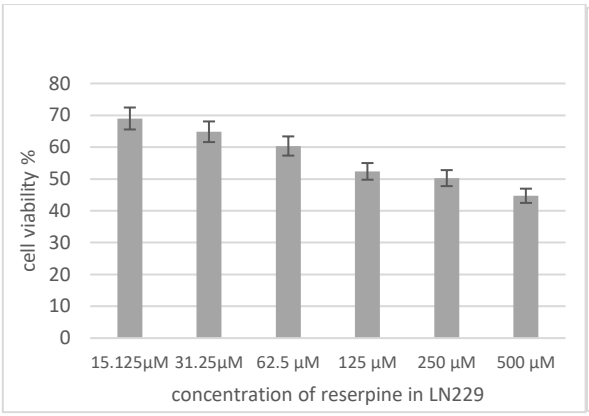
concentration of theobromine in U-87 MG

(F)


80
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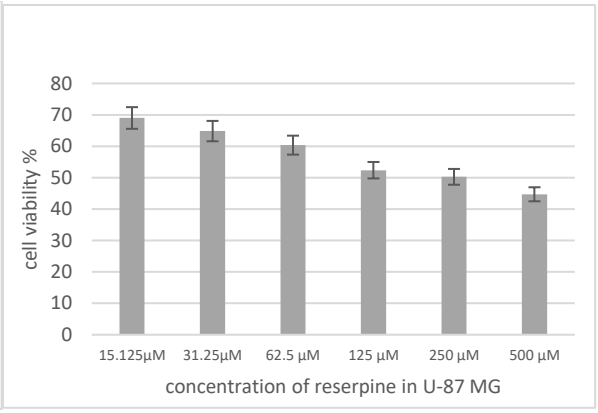
cell viability %
15.125µM 31.25µM 62.5 µM 125 µM 250 µM 500 µM
concentration of reserpine in LN229

(G)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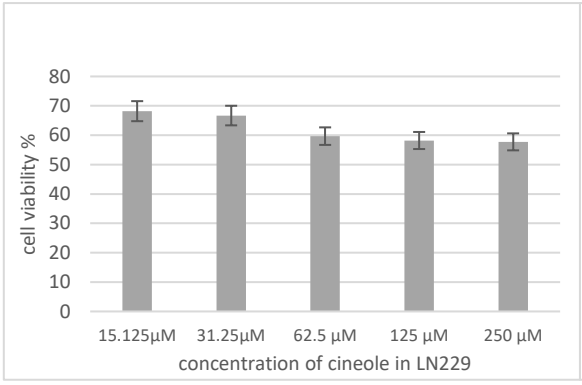
15.125µM 31.25µM 62.5 µM 125 µM 250 µM 500 µM
concentration of reserpine in U-87 MG

(H)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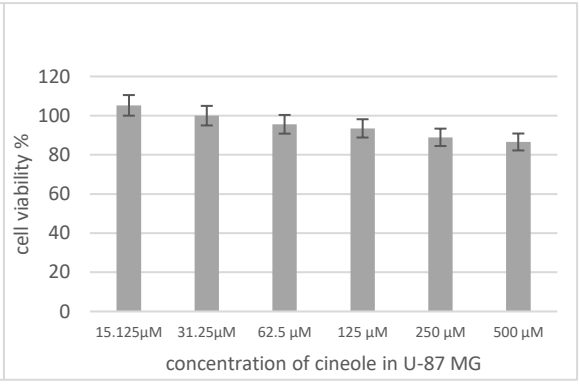
cell viability %
15.125µM 31.25µM 62.5 µM 125 µM 250 µM
concentration of cineole in LN229

(I)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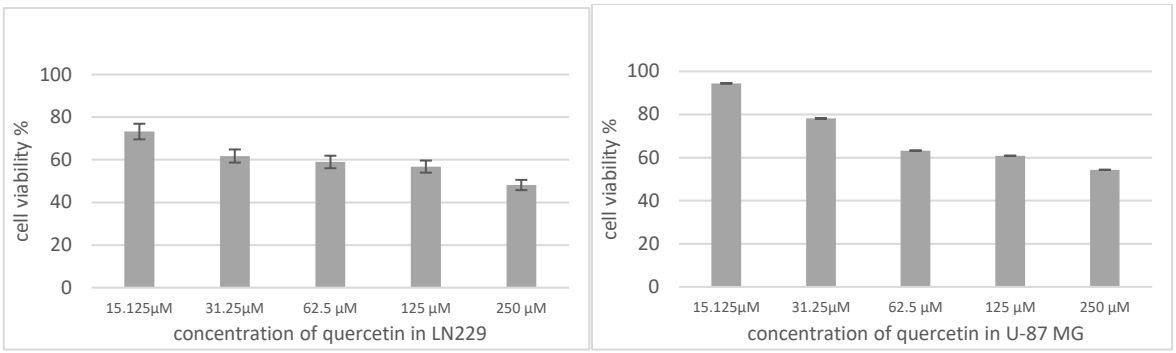
cell viability %
15.125µM 31.25µM 62.5 µM 125 µM 250 µM 500 µM
concentration of cineole in U-87 MG

(J)




(K) (L)

**Figure 1**: The cytotoxicity of single compounds in LN229 and U-87 cell line (A-B) colchicine, (C-D) piperine, (E-F) theobromine, (G-H) reserpine, (I-J) cineole and (K-L) quercetin

**Table 1**: **The $IC_{50}$ of single compounds in LN229 and U-87 cell line**

| Compound | LN229 | U-87 MG |
|---|---|---|
| **Colchicine** | 52 ± 2.3 µM | 89.12 ± 1.7 µM |
| **Piperine** | 182 ± 12.3 µM | N.D. |
| **Theobromine** | 234.1 ± 7.4 µM | N.D. |
| **Reserpine** | 230.4 ± 8.3 µM | 218.7 ± 4.1 µM |
| **Cineole** | N.D. | N.D. |
| **Quercetin** | 79.25 ± 4.2 µM | 331.13 ± 20.1 µM |

The cytotoxic effects of selected phytocompounds, including colchicine, piperine, theobromine, reserpine, cineole, and quercetin, were assessed on LN229 and U-87 MG glioblastoma cell lines using the MTT assay. The results of these experiments are presented in the bar graphs (Figure 1A-L) and summarized in Table 1.

**Cytotoxicity of Phytocompounds**

Dose-dependent cytotoxicity was observed for some testedcompounds. Colchicine displayed significant cytotoxic effects on both LN229 and U-87 MG cells, with $IC_{50}$ values of 52 ± 2.3 µM and 89.12 ± 1.7 µM, respectively. Piperine showed moderate cytotoxicity on LN229, with $IC_{50}$ values of 182 ± 12.3 µM but N.D. in U-87 MG cells. Quercetin demonstrated selective cytotoxicity, being more effective against LN229 cells ($IC_{50}$ = 79.25 ± 4.2 µM) compared to U-87 MG cells ($IC_{50}$ = 331.13 ± 20.1 µM).

Colchicine inhibits microtubule polymerization, disrupting mitotic spindle formation, leading to mitotic arrest and apoptosis in cancer cells [13]. Glioblastoma, reliant on angiogenesis for rapid growth, may benefit from colchicine's ability to disrupt its blood supply [14-16]. The colchicine derivative AD1 showed promise as a glioblastoma treatment by inhibiting cell proliferation, reducing viability in U-87 MG and U373 MG cells, increasing ROS levels, and inducing autophagy. In vivo, AD1 suppressed glioma growth in a rat model with intermittent intravenous administration. Additionally,

colchicine may overcome multidrug resistance and sensitize glioblastoma cells to radiotherapy and chemotherapy [17].

Quercetin shows promise in glioblastoma treatment by modulating cancer-related pathways with minimal toxicity [18]. It induces apoptosis via intrinsic and extrinsic pathways, regulates BAX and Bcl-2 proteins [19], and targets STAT3 and NF-κBsignaling crucial for glioblastoma survival [20]. Quercetin also inhibits EMT, reducing invasiveness, and exhibits anti-angiogenic effects by downregulating VEGF, impairing tumor vascular supply [21]. Its ability to cross the blood-brain barrier and accumulate in brain tissue enhances its potential as a glioblastoma therapy [22]. Additionally, its antioxidant properties reduce oxidative damage, boosting the efficacy of radiation and chemotherapy [23].

The compounds piperine, theobromine, and cineole did not exhibit measurable cytotoxicity under the tested concentrations in U-87 MG cells. The absence of significant activity suggests either a limited therapeutic window or lower potency of these compounds against glioblastoma cells within the experimental parameters [24, 25].

Among the tested compounds, colchicine showed the highest potency against both glioblastoma cell lines, indicating its potential for therapeutic applications. The higher $IC_{50}$ values for piperine and quercetin in U-87 MG cells compared to LN229 cells suggest cell-line-specific responses, likely due to differences in molecular and genetic profiles of the two glioblastoma models.

**Target prediction analysis**

The interaction profiles of the phytocompounds—colchicine, reserpine and quercetin were analyzedsince these three were found to be cytotoxic to both the cell lines. The study has helped to identify their potential target protein classes, as depicted in the pie charts (Figure 2).

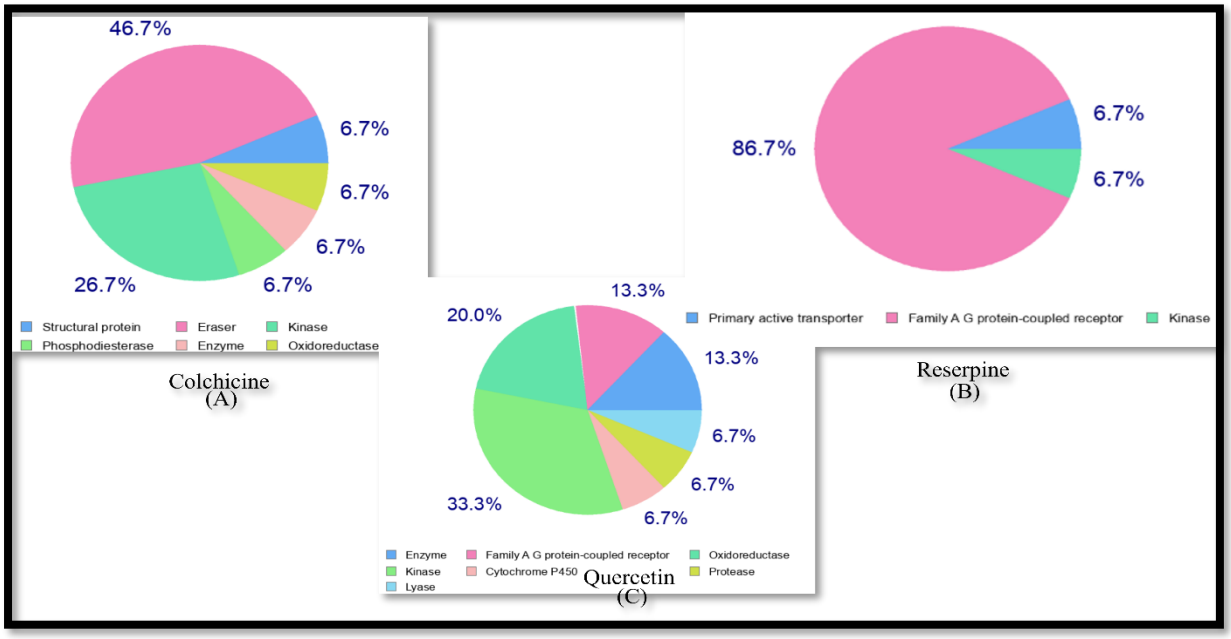


**Figure 2**: Depiction of target prediction of phytocompounds (A)colchicine (B) reserpine (C)quercetin analyzed through Swiss Target prediction tool

Colchicine primarily seemed to interact with structural proteins (46.7%), highlighting its well-documented role in disrupting microtubule dynamics, a process vital for mitotic spindle formation during cell division [26]. By destabilizing microtubules, colchicine can effectively inhibit glioblastoma cell proliferation and induce apoptosis [26]. Its interaction with oxidoreductases (26.7%) suggests additional roles in regulating oxidative stress, which is a hallmark of cancer metabolism. The observed interactions with kinases and phosphodiesterases (6.7% each) indicate that colchicine may also modulate signaling pathways involved in cell survival, making it a multifaceted agent against tumor growth.

Reserpine exhibited a unique interaction profile, predominantly targeting Family A G protein-coupled receptors (86.7%). These receptors are central to regulating neurotransmitter pathways and cell signaling cascades associated with glioblastoma's aggressive phenotype [27]. By inhibiting these receptors, reserpine may reduce the invasive potential of glioblastoma cells and suppress tumor-induced angiogenesis. Its limited interactions with kinases and primary active transporters (6.7% each) indicate potential complementary roles in modulating cellular transport and phosphorylation events, which may indirectly affect tumor progression.

Quercetin indicated the broadest interaction profile, with significant involvement of cytochrome P450 enzymes (33.3%) and Family A G protein-coupled receptors (20%). These interactions highlight quercetin's potential to regulate cellular metabolism and influence critical signaling pathways [28]. Cytochrome P450 enzymes are crucial for drug metabolism, and their interaction with quercetin suggests that it might modulate oxidative stress and detoxification pathways in glioblastoma cells [29]. The interactions with oxidoreductases, nuclear receptors, and lysases (6.7% each) further underscore quercetin's ability to induce apoptosis, inhibit inflammation, and interfere with tumor progression.

**Enrichment analysis**

The enrichment analysis conducted for three phytocompounds- colchicine, reserpine and quercetin revealed several significant biological pathways influenced by these compounds. The results highlight their potential therapeutic roles in various cellular and molecular processes, particularly in the context of glioblastoma (GB).

The biological processes enriched and targeted by colchicine in highlightpotential disruptions in signaling and metabolic regulation in glioblastoma cells after treatment (Figure 3). Protein autophosphorylation and peptidyl-serine/tyrosine modification indicated interference with protein kinase activity, particularly in pathways like PI3K/AKT and MAPK, which are crucial for cell survival and proliferation. Processes such as muscle cell proliferation and rhythmic processes suggest potential dysregulation of the cell cycle or intercellular communication. Notably, the enrichment

of reactive oxygen species (ROS) metabolic processes indicates increased oxidative stress, which may lead to apoptosis or stress-induced cell death. Additionally, disruption of positive regulation of MAPK cascade and protein localization suggests impaired signaling and protein function. Together, these findings suggest that the treatment could inhibit critical survival pathways, increase cellular stress, and potentially reduce glioblastoma proliferation.

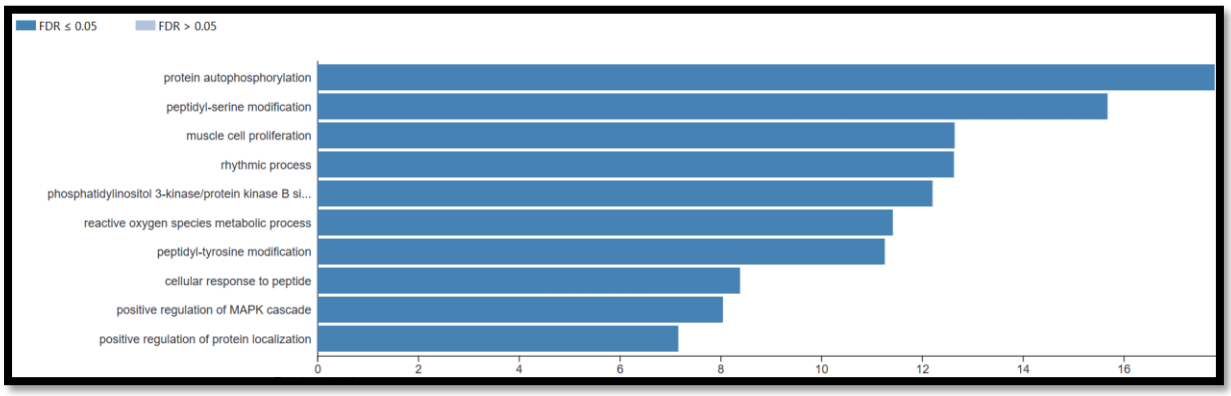



**Figure 3**: Functional enrichment of target genes of colchicine

Reserpine is enriched in adrenergic receptor signaling pathways, emphasizing its role in neurotransmitter modulation and glioblastoma cell responses post-treatment [30]. Disruption of adrenergic signaling, crucial for proliferation and the tumor microenvironment, may impair cell survival and communication. Processes such as vascular regulation, angiogenesis, and GPCR signaling, including phospholipase C activation, suggest impaired tumor growth and signaling. The enrichment of stress response pathways, including xenobiotic stimuli, highlights reduced glioblastoma adaptability and survival [31].

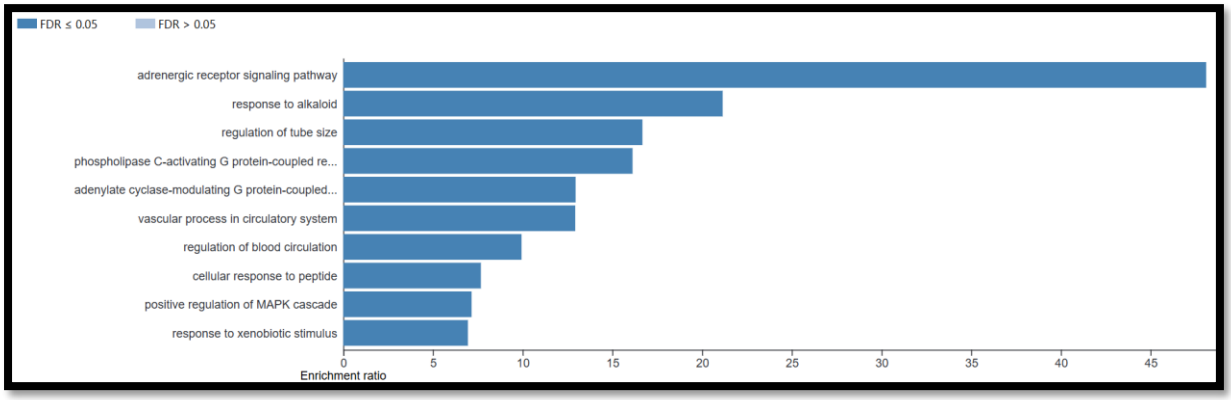



**Figure 4**: Functional enrichment of target genes of reserpine

Quercetin seemed to enrich pathways such as one-carbon metabolism, amyloid-beta response, and secondary metabolism, focusing on processes critical for glioblastoma survival [32]. Enrichment in one-carbon metabolism suggests disruption of nucleotide synthesis and energy production, impairing proliferation. Amyloid-beta and oxidative stress responses indicate increased cellular stress, triggering apoptosis [33]. Disruption

of secondary and icosanoid metabolism highlights interference with lipid metabolism and inflammatory responses vital for tumor survival. Enrichment in protein autophosphorylation and PI3K/AKT signaling suggests inhibition of key pathways driving progression and resistance. These effects collectively impair metabolism, induce stress, and disrupt survival pathways, reducing tumor growth and resilience [34, 35].

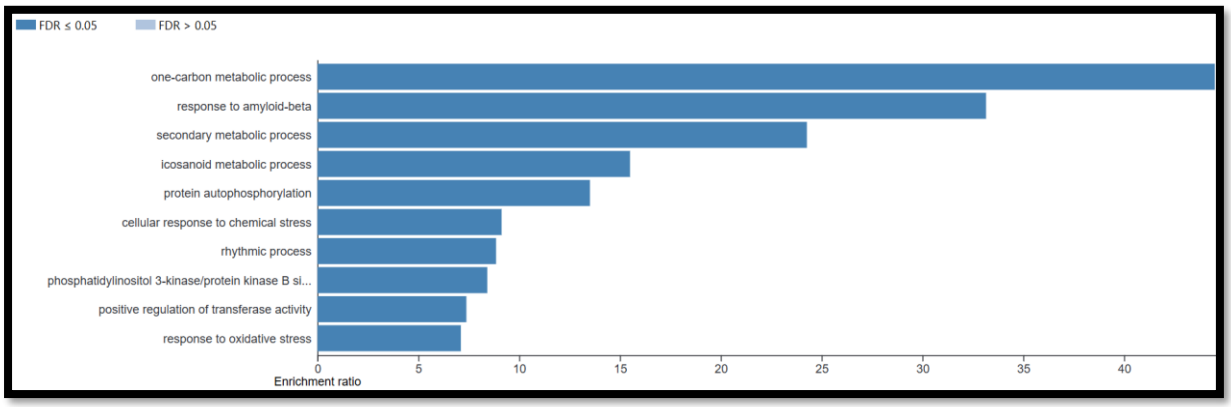



**Figure 5**: Functional enrichment of target genes of quercetin

Pathways related to oxidative stress and cellular signaling, such as ROS metabolism and MAPK cascade regulation, were seemed to be enriched for colchicine and quercetin. These processes are crucial in GB pathogenesis, as they influence cell proliferation, survival, and resistance to apoptosis. Moreover, neurotransmitter modulation, prominently observed in reserpine, highlights its potential neuroprotective role by altering tumor microenvironment dynamics.

While the findings provide significant insights into the potential roles of these phytocompounds, further experimental validation in GB models is required to establish their precise mechanisms of action. These results lay the groundwork for future studies focusing on the therapeutic applications of phytocompounds in GB treatment.

## Conclusion

Colchicine, reserpine, and quercetin demonstrated notable cytotoxicity against glioblastoma cell lines, with colchicine showing the highest potency ($IC_{50}$ of 52 ± 2.3 µM in LN229 cells and 89.12 ± 1.7 µM in U-87 MG cells).Thepossible mechanism of inhibiting GBcell growth was through varied mechanisms, including disruption of microtubule dynamics, oxidative stress, metabolism, and signaling pathways. Colchicine showed the highest potency, while reserpine and quercetin offer additional benefits by modulating angiogenesis, neurotransmitter pathways, and tumor survival. Further in vivo studies and exploration of synergistic effects are needed to confirm their therapeutic value and optimize their clinical application.

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