

Integrative Bioinformatics Analysis of Boswellic Acid–Responsive Genes and Pathways from Medicinal Plant *Boswellia serrata* Implicated in Alzheimer's Disease

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Abstract

Boswellic acids, the major bioactive constituents of *Boswellia* species, have gained increasing attention due to their anti-inflammatory and neuroprotective properties. Considering the growing prevalence of Alzheimer's disease (AD) and the limited effectiveness of current therapeutic approaches, identifying novel molecular targets influenced by natural compounds has become an important research priority. This study employed an integrative bioinformatics framework to characterize genes and pathways modulated by different boswellic acid derivatives, including boswellic acid, 11-keto-boswellic acid, and acetyl-11-keto-boswellic acid. Gene mining and cross-referencing with Alzheimer's-related datasets revealed multiple target genes associated with apoptosis, oxidative stress regulation, inflammation, and autophagy. Chromosomal mapping indicated that chromosomes 1, 14, 17, and 18 harbor key genes—including BCL2, BCL2L1, and TNF—that function as central regulatory hubs in apoptosis and cytokine-mediated signaling. Phylogenetic clustering performed using MEGA demonstrated that boswellic-acid-responsive genes form distinct functional groups related to caspase activation, MAPK signaling, mitochondrial stress, and autophagy regulation. Enrichment analysis further showed significant involvement of these genes in pathways such as Spinocerebellar Ataxia and Autophagy, suggesting potential roles in neuronal survival and stability. A network pathway map generated in Python illustrated multi-target interactions across apoptosis, inflammation, oxidative stress, and cell-cycle control, emphasizing the coordinated regulatory effects of boswellic acids. Collectively, these findings highlight the potential of boswellic acids to modulate interconnected molecular processes relevant to AD pathology. The identified candidate genes and pathways provide a strong basis for future experimental validation and support the potential development of boswellic-acid-based therapeutic strategies for neurodegenerative diseases.

Introduction

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), are characterized by the progressive loss of neuronal structure and function, resulting in cognitive and motor impairments. Among the primary mechanisms driving neuronal death are oxidative stress, neuroinflammation, and apoptosis (Doke et al., 2024; de Oliveira et al., 2014). Conventional pharmacological treatments mainly provide symptomatic relief and fail to halt or reverse neurodegeneration, prompting growing interest in natural compounds with antioxidant and anti-inflammatory properties as potential neuroprotective agents (Theofanous & Kourti, 2022).

Frankincense, derived from *Boswellia serrata*, has been traditionally utilized in Ayurvedic and Persian medicine for its anti-inflammatory, wound-healing, and cognitive-enhancing effects. Its bioactive constituents, collectively known as boswellic acids, exhibit a broad spectrum of biological activities, including antioxidant, anti-cancer, and neuroprotective effects (Phukan et al., 2023). In particular, the antioxidant properties of *Boswellia* resin can help mitigate oxidative stress in neuronal cells, restore redox balance, and potentially slow the progression of neurodegenerative diseases (Theofanous & Kourti, 2022).

The anti-inflammatory effects of boswellic acids also play a crucial role in counteracting neuroinflammation, a hallmark of AD and PD pathology, thereby helping preserve neuronal integrity and function (Phukan et al., 2023; Karvandi et al., 2023). Although current pharmacological therapies focus primarily on symptom management, natural compounds like *Boswellia* offer a more holistic approach to neuroprotection. However, clinical translation is limited by pharmacokinetic challenges, necessitating further research on dosing, combinations, and innovative delivery methods, such as nanotechnology, to enhance therapeutic efficacy in neurodegenerative diseases (Theofanous & Kourti, 2022; Phukan et al., 2023).

Acetyl-11-keto- β -boswellic acid (AKBA) has emerged as a prominent neuroprotective compound in the context of neurodegenerative diseases (NDs), exerting its effects through modulation of multiple molecular targets. Key pathways influenced by AKBA include NF- κ B, which regulates inflammation and apoptosis, and Nrf2/HO-1, which enhances antioxidant defenses and protects against oxidative and ischemic injury (Takada et al., 2006; Ding et al., 2015). Integrative bioinformatics and network analyses have further highlighted the gene networks and molecular interactions impacted by AKBA, underscoring its multifaceted role in neuronal protection.

AKBA exerts neuroprotective effects through both anti-inflammatory and antioxidant mechanisms. It reduces the levels of inflammatory markers and modulates microRNA-155, which is closely linked to neuroinflammation, while simultaneously upregulating HO-1 expression to mitigate oxidative stress in neuronal cells (Sayed et al., 2018; Ding et al., 2015). In experimental models, AKBA has demonstrated potential in reversing cognitive dysfunction induced by inflammatory stimuli, indicating its therapeutic promise for preserving cognitive function in NDs (Sayed et al., 2018).

Despite its potent pharmacological activities, the molecular targets and gene networks influenced by different boswellic acid derivatives, including AKBA, remain incompletely characterized in human neurological contexts. Therefore, this study aims to identify human genes associated with major boswellic acid derivatives and explore their potential involvement in neurodegenerative pathways through integrative bioinformatics and network-based analyses. The findings are expected to provide novel insights into the mechanisms by which *Boswellia* resin compounds contribute to neuroprotection, inflammation regulation, and oxidative stress mitigation (Javadi, 2023).

The identification of active phytochemical constituents in *Boswellia serrata* resin has revealed several key compounds, particularly boswellic acid derivatives, which are widely recognized for their medicinal properties. The principal constituents include β -boswellic acid, 11-keto-boswellic acid, acetyl-11-keto-boswellic acid (AKBA), and α -boswellic acid, each contributing to the resin's anti-inflammatory and therapeutic effects (Siddiqui, 2011; Sharifi et al., 2023; Singh et al., 2024).

Among these derivatives, β -boswellic acid is well-known for its anti-inflammatory properties and its ability to inhibit pro-inflammatory enzymes, while 11-keto-boswellic acid also exhibits significant anti-inflammatory activity, enhancing the overall therapeutic profile of *Boswellia serrata* (Siddiqui, 2011). Acetyl-11-keto-boswellic acid (AKBA) is recognized as the most potent inhibitor of 5-lipoxygenase,

playing a central role in managing inflammation and oxidative stress (Siddiqui, 2011; Sharifi et al., 2023). Although α -boswellic acid is less studied, it contributes to the broader spectrum of boswellic acids responsible for the resin's efficacy (Singh et al., 2024).

Traditionally, *Boswellia serrata* has been employed in Ayurvedic and Unani medicine for treating a range of ailments, including respiratory disorders and inflammatory conditions (Jana et al., 2020). Contemporary research has further highlighted the protective effects of AKBA, such as its role in mitigating acute kidney injury, demonstrating its potential in modern therapeutic applications (Sharifi et al., 2023). However, the clinical efficacy of *Boswellia serrata* may vary depending on extraction methods and individual patient responses, underscoring the need for additional studies to optimize its use in medical practice.

The aim of the present study is to systematically identify human genes and signaling pathways associated with major boswellic acid derivatives (β -boswellic acid, 11-keto-boswellic acid, acetyl-11-keto-boswellic acid, and α -boswellic acid) using integrated bioinformatics and network analysis tools. This study investigates which of these compounds are most strongly associated with genes involved in oxidative damage, apoptosis, autophagy, and neurodegeneration, thereby providing new insights into the potential neuroprotective mechanisms of *Boswellia* resin.

Materials and Methods

Identification of Active Phytochemical Constituents

The major chemical constituents of *Boswellia serrata* resin were retrieved from three phytochemical databases: Dr. Duke's Phytochemical and Ethnobotanical Database, IMPPAT (Indian Medicinal Plants, Phytochemistry, and Therapeutics) and CTD (Comparative Toxicogenomics Database). From these sources, the principal boswellic acid derivatives were identified, including β -boswellic acid, 11-keto-boswellic acid, acetyl-11-keto-boswellic acid (AKBA), and α -boswellic acid.

Chromosomal Localization and Transcript Information

For each identified gene, the chromosomal location and the number of transcript variants were retrieved from the NCBI Gene databases. This information was used to construct a comprehensive table indicating gene position, transcript diversity, and compound association.

Gene–Compound Interaction Analysis

To identify human genes that interact with each compound, data were collected from the Comparative Toxicogenomics Database (CTD). Each compound name was searched individually, and the corresponding gene–chemical interaction tables were downloaded. Genes associated with oxidative stress, apoptosis, and neurodegenerative processes were selected for further analysis.

Functional Enrichment and Pathway Analysis

To determine the biological pathways and processes associated with these genes, functional enrichment analyses were performed using Enrichr, Metascape, and Cytoscape platforms. The input gene lists were analyzed for enrichment in Gene Ontology (GO) terms and KEGG pathways related to apoptosis, oxidative stress, inflammation, and autophagy. Network visualizations were generated using Cytoscape (v3.9.1), highlighting highly connected “hub” genes with strong chemical interactions.

Heatmap, Network, and Pathway Visualization

To visualize the interactions between active chemical constituents of *Boswellia serrata* and genes associated with oxidative stress, apoptosis, and neurodegenerative processes, several graphical approaches were employed. A heatmap was constructed to display compound-gene interactions, with genes represented on the X-axis and compounds on the Y-axis. Interaction strengths were color-coded across three levels, ranging from low to high intensity, allowing rapid identification of the most significant chemical-gene associations. Heatmaps were generated using either R (ggplot2 or pheatmap) or Python (Seaborn).

Mega Analysis

In the network-based “mega” analysis, instead of chemical interactions, the transcript variants of the identified genes were compared to assess their relationships and potential co-regulation. Nodes in this network represented individual transcript variants, and edges indicated shared features or functional relationships between transcripts. Node size and color were used to highlight transcript diversity and their grouping within specific gene families or functional categories. This approach enabled the identification of patterns of transcript-level connectivity across the genes of interest and was visualized using Cytoscape v3.9.1.

Pathway diagrams

Pathway diagrams were generated to illustrate the biological pathways in which the identified genes and compounds are involved, including apoptosis, oxidative stress, inflammation, and autophagy. Nodes in these diagrams represented genes or compounds, while edges indicated pathway relationships. Color coding was used to distinguish different biological processes, and interaction strength was visually emphasized. Pathway enrichment analyses were performed using Enrichr and Metascape, and the resulting diagrams were visualized with Cytoscape to provide a comprehensive overview of the molecular mechanisms potentially influenced by *Boswellia serrata* constituents. The pathway map was generated using Python with two key libraries: NetworkX for building and organizing the biological interaction network, and Matplotlib for visualizing the graph.

Results and Discussion

Identification of Major Bioactive Compounds in *Boswellia serrata* Resin

The resin of *Boswellia serrata* contains several bioactive compounds, with boswellic acids representing the primary pharmacologically active constituents. Among these, acetyl-11-keto- β -boswellic acid (AKBA) and 11-keto-boswellic acid (KBA) have received particular attention due to their potent anti-inflammatory, antioxidant, and neuroprotective effects [10]. These derivatives have been extensively characterized through phytochemical studies and are consistent with the traditional medicinal use of *Boswellia* resin in Ayurveda and Unani medicine.

Acetyl-11-keto- β -boswellic acid (AKBA): AKBA is a well-established inhibitor of 5-lipoxygenase, a critical enzyme in inflammatory pathways, and has demonstrated significant anti-inflammatory activity. This property underlies its therapeutic potential in conditions such as rheumatoid arthritis and asthma (Siddiqui, 2011). **11-keto-boswellic acid (KBA):** KBA also exhibits strong anti-inflammatory effects and contributes to the overall pharmacological profile of *Boswellia serrata*, reinforcing its traditional and modern therapeutic relevance. **Chronic Inflammatory Diseases:** Boswellic acids have been reported to be effective in managing chronic inflammatory conditions, including inflammatory bowel disease and arthritis. **Neuroprotective Effects:** Recent studies suggest that boswellic acids, particularly AKBA and KBA, may offer neuroprotective benefits, highlighting their potential application in neurological disorders characterized by oxidative stress, apoptosis, and inflammation (Siddiqui, 2011; Salati, 2024). While AKBA and KBA are recognized as the most pharmacologically potent derivatives, other boswellic acids such as β -boswellic acid and α -boswellic acid may act synergistically, contributing to the overall therapeutic effects observed in traditional practices.

Phytochemical data retrieved from Dr. Duke's Phytochemical and Ethnobotanical Database, Knapsack, and IMPPAT consistently indicate that boswellic acids are the dominant bioactive constituents of *Boswellia serrata* resin. The principal derivatives identified include β -boswellic acid, 11-keto-boswellic acid, acetyl-11-keto- β -boswellic acid (AKBA), and α -boswellic acid. Among these, AKBA and KBA are the most pharmacologically active, providing a rational basis for focusing subsequent gene interaction and pathway analyses on these key boswellic acid derivatives. This identification aligns with previous experimental and clinical findings demonstrating their strong anti-inflammatory, antioxidant, and neuroprotective properties (Siddiqui, 2011; Salati, 2024).

Identification of Human Genes Targeted by Boswellic Acid Derivatives

The analysis of gene–compound interactions using the Comparative Toxicogenomics Database (CTD) revealed that different boswellic acid derivatives exhibit distinct yet partially overlapping effects on human genes, particularly in pathways related to apoptosis, oxidative stress, inflammation, and cell survival. These findings provide a molecular basis for the pharmacological activities of *Boswellia serrata*

compounds and highlight their therapeutic potential in diverse biological contexts (Takada et al., 2006; Sun et al., 2020).

β -boswellic acid primarily interacts with genes associated with cell survival and growth, including AKT1, EGFR, TOP1, TOP2A, and VEGFA, suggesting its involvement in proliferative and stress-response pathways (Sun et al., 2020). These interactions support its potential role in modulating cellular homeostasis and resilience under pathological conditions.

In contrast, 11-keto-boswellic acid (KBA) shows strong associations with apoptosis-related genes, particularly members of the caspase family (CASP1–CASP9) and CYCS, indicating a central role in mitochondrial-dependent cell death and intrinsic apoptotic signaling (Li et al., 2018). This aligns with its reported anti-proliferative and cytotoxic effects in various preclinical studies.

AKBA exhibits the broadest gene interaction profile among the tested derivatives, targeting multiple key regulatory genes including CDKN1A, BAX, BCL2, ATG5, BECN1, MAPK1, PARP1, and TNF. These genes collectively regulate oxidative stress, autophagy, inflammatory signaling, and apoptosis, reflecting the multi-target nature of AKBA and its potent pharmacological activity (Takada et al., 2006). The extensive gene coverage of AKBA supports its prominent role in neuroprotection and anti-inflammatory responses.

In comparison, α -boswellic acid interacts primarily with genes involved in antioxidant defense and inflammatory modulation, including GSR, IL1B, and TNF (Lv et al., 2020). This suggests a more focused, yet complementary, effect on redox balance and cytokine-mediated pathways.

These results demonstrate that boswellic acid derivatives possess differential but complementary gene-targeting profiles, with AKBA showing the most extensive multi-target interactions. The overlapping yet distinct patterns of gene regulation highlight the therapeutic versatility of boswellic acids, supporting their role in modulating apoptosis, oxidative stress, inflammation, and autophagy. However, the complexity of these interactions also indicates that biological effects may vary depending on tissue context and disease state, necessitating further experimental validation to fully elucidate the underlying mechanisms.

Association of Boswellic Acid–Targeted Genes with Neurodegenerative Diseases

Enrichment analysis using GeneCards and the Comparative Toxicogenomics Database (CTD) revealed that boswellic acid derivatives target multiple genes critically involved in neurodegenerative disorders, particularly Alzheimer's disease (AD) and Parkinson's disease (PD). Key genes, including CASP3, CASP9, CYCS, BCL2, TNF, EGFR, ATG5, BECN1, and AKT1, are associated with essential pathological processes such as neuronal apoptosis, oxidative stress, neuroinflammation, and dysregulated iron homeostasis. These findings highlight the molecular relevance of boswellic acids and suggest potential therapeutic targets for modulating neuronal survival and homeostasis (Rahman et al., 2020; Liu et al., 2015).

Boswellic acids exhibit multi-target regulatory effects on neuronal cell fate. For example, 11-keto-boswellic acid and acetyl-11-keto- β -boswellic acid (AKBA) modulate apoptotic genes such as CASP3 and BAX, suggesting their role in controlling neuronal apoptosis during AD progression. Simultaneously, these compounds interact with autophagy-related genes, including ATG5 and BECN1, which are essential for clearing damaged proteins and organelles, thereby contributing to neuroprotection. This dual regulation implies that boswellic acids can balance apoptosis and autophagy, offering a nuanced approach to neuronal survival rather than complete inhibition of cell death pathways (Kelly et al., 2020).

While these gene interactions suggest shared molecular mechanisms in AD and PD, it is important to recognize the disease-specific differences and progression patterns. The interplay between genetic predisposition and environmental factors also shapes disease manifestation, emphasizing the complexity of developing effective neuroprotective strategies. Overall, the findings support the therapeutic potential of boswellic acids in modulating key pathways involved in apoptosis, oxidative stress, neuroinflammation, and autophagy, laying a foundation for further experimental and clinical validation (Liu et al., 2015; Rahman et al., 2020).

Chromosomal Distribution and Transcript Variability of Target Genes

Chromosomal mapping based on data from NCBI and Ensembl revealed that boswellic acid-associated target genes are distributed across multiple human chromosomes, with notable enrichment on chromosomes 1, 14, 17, and 18 (Table 1). These chromosomes are recognized for containing genes involved in apoptotic regulation, inflammatory signaling, and oxidative stress responses, which are central mechanisms in the pathogenesis of neurodegenerative diseases (NDs) such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Javadi, 2023; Haghaei et al., 2020). The non-random clustering of these genes suggests a coordinated genomic regulation that may underlie the neuroprotective and anti-inflammatory properties of boswellic acid derivatives.

Among the identified genes, BCL2 on chromosome 14, TNF on chromosome 17, and BCL2L1 on chromosome 18 emerged as central hub genes linking apoptotic and cytokine-mediated signaling pathways, integrating cell survival, inflammation, and programmed cell death (Javadi, 2023). Chromosome 1 was enriched with caspase (CASP) family genes, highlighting its importance in apoptosis and inflammatory regulation relevant to neurodegeneration. In addition, chromosome 11 contributed genes such as CDKN1A, CASP4, and CASP5, associated with p53-mediated oxidative stress pathways, consistent with the reported antioxidant effects of Boswellia-derived compounds. The BAX gene on the X chromosome acts as a critical determinant of apoptotic balance, where the BAX/BCL2 ratio influences neuronal vulnerability and survival in neurodegenerative contexts (Javadi, 2023).

Most boswellic acid-associated genes exhibited multiple transcript variants, ranging from a single transcript to over twenty isoforms, indicating complex transcriptional regulation and potential tissue-specific expression, particularly within the central nervous system. This diversity allows fine-tuned control of apoptosis, inflammation, and oxidative stress in neurons. Overall, the genomic distribution and

functional clustering of these genes across specific chromosomes suggest that boswellic acid derivatives may exert coordinated regulatory effects on neuroprotective pathways. Such coordinated regulation provides a mechanistic basis for the potential therapeutic application of *Boswellia serrata* compounds in managing neurodegenerative diseases, while recognizing that additional genetic and environmental factors may also influence treatment outcomes (Javadi, 2023; Haghaei et al., 2020).

Gene–Chemical Interaction Network and Functional Pathway Enrichment

Network visualization using Enrichr, Metascape, and Cytoscape revealed dense interconnections between boswellic acid–targeted genes and chemicals known to induce cellular stress, inflammation, or apoptosis. Key hub genes, including CASP3, BAX, BCL2, ATG5, EGFR, and TNF, exhibited strong interactions with compounds such as doxorubicin, arsenic trioxide, cisplatin, and lipopolysaccharides. These findings suggest that boswellic acid targets genes involved in apoptosis, oxidative stress response, MAPK signaling, autophagy, and inflammatory pathways, highlighting its potential to modulate signaling networks commonly activated during neurotoxicity and neurodegeneration (Javadi, 2023; Karabat & Tuncer, 2025).

Table 1

, Chromosomal distribution of key genes involved in apoptosis, inflammation, and neurodegeneration-related pathways.

Chromosome	Key Genes Located	Biological Relevance
Chr 1	CASP9, MMP9, AKT3	Involved in apoptosis and inflammatory signaling; chromosome 1 harbors multiple loci implicated in neurodegenerative disorders.
Chr 14	BCL2, MAPK1	Regulates cell survival and MAPK pathways; alterations are linked with Alzheimer’s and Parkinson’s disease.
Chr 17	TNF, MAPK7	Plays a central role in cytokine signaling and neuroinflammation; TNF is a major hub gene in brain inflammation.
Chr 18	BCL2L1 (BCL-XL)	Controls the balance between neuronal survival and apoptosis.
Chr 11	CDKN1A, CASP4, CASP5	Associated with the p53 signaling pathway and oxidative stress response.
Chr 12	CDK2, CCNE1	Involved in cell cycle regulation and neuronal precursor division.
Chr X	BAX	A key pro-apoptotic gene interacting with BCL2 at the mitochondrial membrane.

The hub genes identified—CASP3, BAX, BCL2, ATG5, EGFR, and TNF—play pivotal roles in regulating neuronal survival, apoptosis, and inflammatory signaling, all of which are critical in neurodegenerative disease progression. Their strong interactions with cytotoxic and pro-inflammatory compounds suggest that boswellic acid may exert neuroprotective effects by modulating these pathways, potentially

reducing oxidative damage and aberrant apoptosis in neuronal cells (Javadi, 2023). Additionally, the interconnected nature of these genes across multiple pathways underscores the multi-target action of boswellic acids, supporting a systems-level neuroprotective mechanism.

Boswellic acid demonstrates anti-inflammatory, antioxidant, and anti-apoptotic properties, which may counteract neurodegenerative processes such as those observed in Alzheimer's and Parkinson's disease [21, 24]. Furthermore, its synergistic interactions with chemotherapeutic agents suggest potential dual roles in cancer modulation and neuroprotection (Karabat & Tuncer, 2025). Despite these promising insights, the complexity of neurodegenerative diseases and the multifactorial nature of neuronal stress necessitate further experimental and clinical studies to fully elucidate the therapeutic mechanisms, dose–response relationships, and potential for translational application of boswellic acids in neurodegenerative contexts..

Gene–Pathway Network Analysis

To further investigate the biological relevance of genes targeted by boswellic acid derivatives, a gene–pathway interaction network was constructed using Metascape and visualized in Cytoscape (Fig. 1). The network revealed several highly interconnected modules linking apoptotic and stress-related genes—including CASP3, CASP8, CASP9, BAX, and BCL2—with key signaling pathways such as Apoptosis, p53 signaling, Pathways in Cancer, and Hepatitis B signaling. Genes involved in oxidative and inflammatory responses, including AKT1, MAPK1, MAPK3, and TNF, were additionally associated with the Lipid and Atherosclerosis pathway, suggesting their dual roles in metabolic regulation and neuroinflammation. Notably, CASP3, MAPK1, and BCL2 emerged as major hub genes bridging multiple pathways, highlighting their central role in coordinating apoptosis, survival, and oxidative balance. These interconnections support the hypothesis that boswellic acid derivatives exert neuroprotective effects by simultaneously modulating p53-dependent apoptotic regulation, MAPK-mediated stress signaling, and TNF-driven inflammatory cascades (Srivastava et al., 2018; Gupta et al., 2021; Guo et al., 2015).

The analysis identified apoptotic genes (CASP3, CASP8, BCL2) as crucial regulators of programmed cell death, which is central to neuronal survival and neurodegenerative disease progression. Stress-response genes, including AKT1 and MAPK1, were linked to oxidative stress and inflammatory signaling pathways, underscoring their role in neuroprotection. The identification of CASP3, MAPK1, and BCL2 as hub genes further emphasizes their integrative function, connecting apoptosis, oxidative stress, and inflammatory pathways. The network illustrates that boswellic acid derivatives act through multi-target mechanisms, potentially providing coordinated modulation of cellular stress responses and apoptotic regulation in neurodegenerative contexts (Srivastava et al., 2018; Gupta et al., 2021).

The constructed network provides mechanistic insight into how boswellic acid compounds may protect neurons by simultaneously influencing apoptosis, oxidative stress, and inflammatory pathways. Specifically, modulation of p53 signaling, MAPK-mediated stress response, and TNF-driven inflammation suggests a holistic, multi-pathway approach to neuroprotection, rather than targeting a single molecular axis. However, the findings also highlight that dysregulation of these pathways can contribute to

neurodegeneration, indicating that therapeutic interventions should aim for balanced modulation of apoptosis, oxidative stress, and inflammation to optimize neuroprotective outcomes (Guo et al., 2015; Srivastava et al., 2018; Gupta et al., 2021).

Functional Enrichment of Apoptosis-Related Genes

To elucidate the biological processes modulated by boswellic acid-associated targets, a Gene Ontology (GO) functional enrichment network was constructed (Fig. 2). The analysis revealed that most identified genes are involved in apoptotic and inflammatory signaling pathways. Key enriched GO terms included “apoptotic process (GO:0006915)”, “negative regulation of apoptotic process (GO:0043066)”, “cytokine-mediated signaling pathway (GO:0019221)”, and “extrinsic apoptotic signaling pathway (GO:0097191)”. Central pro-apoptotic genes such as CASP3, CASP8, CASP9, and BAX were strongly linked to intrinsic and extrinsic apoptosis cascades, whereas anti-apoptotic regulators BCL2 and BCL2L1 (BCL-XL) were associated with cell survival and anti-apoptotic responses. Additionally, TNF and AKT1 participated in cytokine-mediated signaling, indicating dual roles in both apoptosis and inflammation. Peripheral genes including MMP9, VEGFA, and SQSTM1 occupied secondary nodes, reflecting their indirect involvement in oxidative stress and cell-death modulation (Javadi, 2023; Bhosle & Wadher, 2024).

These findings suggest that boswellic acid derivatives exert a coordinated regulation of neuronal apoptosis by balancing pro-apoptotic (BAX, CASP3/8/9) and anti-apoptotic (BCL2, BCL2L1, AKT1) gene activity. Rather than completely inhibiting apoptosis, these compounds appear to fine-tune cell death pathways, maintaining neuronal survival while preventing excessive apoptotic activity. This mechanistic balance underpins the neuroprotective and anti-inflammatory potential of boswellic acids, aligning with previous evidence demonstrating their capacity to modulate neuronal stress responses and reduce neuroinflammation (Liu et al., 2002).

Peripheral and indirect gene targets, including MMP9, VEGFA, and SQSTM1, highlight additional modulatory effects on oxidative stress, autophagy, and structural remodeling pathways. These secondary interactions suggest that boswellic acids may also support cellular clearance, vascular stability, and tissue repair processes, which are critical in neurodegenerative conditions such as Alzheimer’s and Parkinson’s disease. Nevertheless, the complexity of apoptotic and inflammatory regulation warrants further research to fully understand the therapeutic implications and potential unintended effects of boswellic acid derivatives in neuronal systems (Javadi, 2023; Liu et al., 2002; Bhosle & Wadher, 2024).

Analysis of Enrichment Results for Genes Affected by *Boswellia* Active Compounds

Based on enrichment analysis and heatmap visualization, the genes influenced by *Boswellia* active compounds, particularly boswellic acids, are enriched in multiple pathways critical for neuronal function and brain health (Fig. 3). Pathways such as Spinocerebellar Ataxia and Autophagy indicate a potential regulatory role of *Boswellia* in neurodegenerative disorders. Spinocerebellar Ataxia is typically associated with neuronal degeneration, and its enrichment suggests that *Boswellia*-targeted genes may contribute

to neuronal stability, survival, and the maintenance of proper cellular homeostasis. Additionally, pathways related to apoptosis and necroptosis underscore the involvement of *Boswellia* in regulating programmed cell death, supporting the clearance of damaged or toxic proteins—a key mechanism implicated in Alzheimer’s and Parkinson’s diseases (Bhosle & Wadher, 2024; Sarkar & Rubinsztein, 2008).

Autophagy emerged as a central pathway, highlighting its role in protein quality control and neuronal health. Boswellic acids may enhance autophagic processes, facilitating the removal of aggregate-prone proteins that accumulate in neurodegenerative conditions such as Spinocerebellar Ataxia, Alzheimer’s, and Huntington’s disease. This mechanism aligns with evidence showing that dysregulation of autophagy contributes to neuronal dysfunction, while targeted modulation can preserve neuronal viability and homeostasis (Marcelo et al., 2022; Sarkar & Rubinsztein, 2008). Furthermore, genes associated with HIF-1 signaling and cellular responses to oxidative stress suggest that *Boswellia* can bolster neuronal resistance to hypoxic and oxidative insults, which are common stressors in neurodegeneration.

In addition to autophagy, *Boswellia* exhibits anti-inflammatory and antioxidant effects, modulating pathways such as TNF and Interleukin-18 signaling to mitigate neuroinflammation, a major contributor to ongoing neuronal damage. Other enriched pathways, including Animal Organ Regeneration and Cellular Component Biogenesis, indicate potential roles in promoting neuronal repair and structural organization. Collectively, these findings suggest that *Boswellia* compounds exert neuroprotective effects through multiple mechanisms: reducing neuroinflammation, enhancing autophagy, counteracting oxidative stress, preventing excessive neuronal death, and supporting regeneration. Such multi-target activity supports their potential therapeutic relevance for neurodegenerative diseases and cognitive disorders associated with hippocampal dysfunction (Kazmi et al., 2011; Alawiyah et al., 2023; Bhosle & Wadher, 2024).

MEGA Analysis of Transcript-Level Relationships

MEGA-based analysis focusing on transcript variants revealed clear functional and evolutionary clustering among genes associated with apoptosis, oxidative stress, inflammation, and autophagy (Fig. 4). Apoptosis-related genes, including members of the caspase family (CASP3, CASP8, CASP9), CYCS, and the BAX/BCL2 regulatory axis, formed tightly interconnected clusters strongly linked to mitochondrial regulation and intrinsic apoptotic signaling. The close evolutionary conservation observed within this cluster suggests that these genes represent functionally constrained targets that play a central role in neuronal cell fate determination.

Oxidative stress–related genes, such as CAT and GSR, grouped into a distinct module, reflecting their coordinated involvement in redox homeostasis and detoxification processes. This clustering highlights the functional coupling of antioxidant defense mechanisms and supports the hypothesis that boswellic acids may enhance cellular resilience against reactive oxygen species, a major contributor to neurodegenerative pathology.

Inflammatory mediators, including TNF- α and IL-1 β , were mapped to a separate but strongly interconnected module that showed extensive crosstalk with both apoptotic and MAPK signaling pathways. This connectivity underscores the pivotal role of inflammatory signaling in linking immune activation to neuronal stress responses and suggests that boswellic acids may exert anti-inflammatory effects by modulating upstream cytokine-driven cascades that converge on apoptosis and stress-related pathways.

Autophagy-related genes (ATG5, BECN1, and SQSTM1) appeared more dispersed within the network but retained moderate connectivity with oxidative stress and apoptosis nodes. This distribution suggests that autophagy may be indirectly regulated through upstream modulation of redox balance and mitochondrial integrity rather than through direct targeting of autophagic machinery. Such indirect regulation is consistent with the role of autophagy as an adaptive, context-dependent survival mechanism in neurodegenerative conditions.

Integration of the MEGA-derived gene clusters with pathway mapping further demonstrated that boswellic acids—particularly acetyl-11-keto-boswellic acid (AKBA), 11-keto-boswellic acid (KBA), and α -boswellic acid—interact with a broad network of Alzheimer's disease-related genes involved in inflammation, apoptosis, oxidative stress, autophagy, and MAPK-mediated cell-cycle regulation. Several highly connected hub genes, including TNF- α , IL-1 β , CASP3, CASP8, BAX, BCL2, CAT, MAPK family members, ATG5, and BECN1, were consistently positioned at the intersection of multiple pathways, indicating that boswellic acids act through multi-target, network-based mechanisms rather than a single linear signaling route.

Overall, combined MEGA and pathway analyses indicate that boswellic acids predominantly modulate a conserved inflammation–apoptosis–oxidative stress triad, with secondary effects on autophagy and cell-cycle regulation, highlighting their multi-target neuroprotective potential in neurodegenerative diseases such as Alzheimer's. These compounds mitigate neuroinflammation by inhibiting pro-inflammatory cytokines, thereby reducing neuronal damage and promoting cell survival (Javadi, 2023). They regulate apoptosis by stabilizing mitochondrial function, preventing the release of pro-apoptotic factors such as BAX and caspases, and maintaining cellular integrity, while also reducing Tau phosphorylation and amyloid- β accumulation, key contributors to Alzheimer's pathology (Bhosle & Wadher, 2024; Javadi, 2023). Furthermore, boswellic acids enhance antioxidant defenses, decreasing oxidative stress and protecting neurons from free radical-induced injury, which supports cognitive function and neuronal viability (Ameen et al., 2017; Bhosle & Wadher, 2024). Collectively, these coordinated actions suggest that Boswellia-derived compounds exert neuroprotection through integrated regulation of apoptosis, inflammation, and oxidative stress, aligning with the complex, multifactorial mechanisms underlying neurodegenerative disease progression.

Pathway Map Analysis of Boswellic Acid–Related Targets

The pathway map generated using NetworkX and visualized with Matplotlib demonstrates that boswellic acid derivatives interact with Alzheimer's disease (AD)–related genes across multiple biological pathways, including inflammation, apoptosis, oxidative stress, autophagy, and MAPK-mediated cell-cycle regulation (Fig. 5). In the network, pathway hubs functioned as central organizing nodes, each linking to clusters of functionally related genes, while boswellic acid compounds were positioned on the periphery, connected to their respective targets. This arrangement illustrates that these compounds do not act through a single linear pathway but influence multiple mechanistic axes simultaneously, reflecting the multifactorial nature of AD (Haghaei et al., 2020).

Boswellic acids exhibit anti-inflammatory, antioxidant, and anti-apoptotic effects, which contribute to their neuroprotective potential by modulating key genes involved in neuronal survival and stress responses (Javadi, 2023; Hu et al., 2017). The interaction of boswellic acids with hub genes across different pathways highlights their ability to coordinate network-level regulation, potentially mitigating neuroinflammation, oxidative damage, and apoptotic imbalance—processes central to AD progression.

The multi-target activity of boswellic acids underscores their relevance as potential therapeutic agents and supports their consideration as lead compounds in drug development for neurodegenerative diseases (Haghaei et al., 2020). However, this broad interaction profile also presents challenges in precisely defining their mechanisms of action, emphasizing the need for further research to map specific pathways influenced by boswellic acids and optimize their therapeutic application in AD.

Conclusion

Boswellia serrata resin contains several bioactive compounds, among which boswellic acid derivatives—particularly acetyl-11-keto- β -boswellic acid (AKBA) and 11-keto-boswellic acid (KBA)—exhibit the most potent pharmacological activities. These compounds demonstrate anti-inflammatory, antioxidant, anti-apoptotic, and neuroprotective effects, supporting both traditional medicinal applications and contemporary therapeutic potential. Through a comprehensive gene–compound interaction analysis, key human genes were identified that are regulated by boswellic acids, including genes involved in apoptosis (CASP3, CASP8, CASP9, BAX, BCL2), oxidative stress response (CAT, GSR, AKT1), inflammation (TNF, IL1B), and autophagy (ATG5, BECN1, SQSTM1). The differential yet complementary targeting of these genes suggests a multi-target mechanism, which allows fine-tuned modulation of neuronal survival, inflammation, and oxidative homeostasis.

Enrichment and pathway analyses revealed that boswellic acids significantly influence pathways implicated in neurodegenerative disorders such as Alzheimer's and Parkinson's disease, including apoptosis, oxidative stress, autophagy, MAPK signaling, and inflammatory cascades. MEGA and transcript-level analyses highlighted functional clustering and evolutionary conservation among genes regulating neuronal cell fate, emphasizing the potential for coordinated neuroprotective effects. The integration of gene–pathway networks further demonstrated that boswellic acids act through multiple

hubs and interconnected pathways rather than a single linear route, indicating a systems-level mode of action.

Overall, the findings suggest that *Boswellia serrata* derivatives, particularly AKBA and KBA, exert multifaceted neuroprotective effects by balancing apoptosis, reducing oxidative stress, modulating inflammatory signaling, and promoting autophagy. These properties position boswellic acids as promising candidates for therapeutic intervention in neurodegenerative diseases, providing a molecular basis for their traditional use and a rationale for further experimental and clinical studies to explore their translational potential.

Declarations

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Author Contributions

Elmira Ziya Motalebipour contributed to all aspects of this work, including: conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing—original draft, writing—review & editing, visualization, supervision, and project administration.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The author declare no competing interests.

Clinical trial number

Not applicable

Ethics and Consent to Participate declarations

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Figures

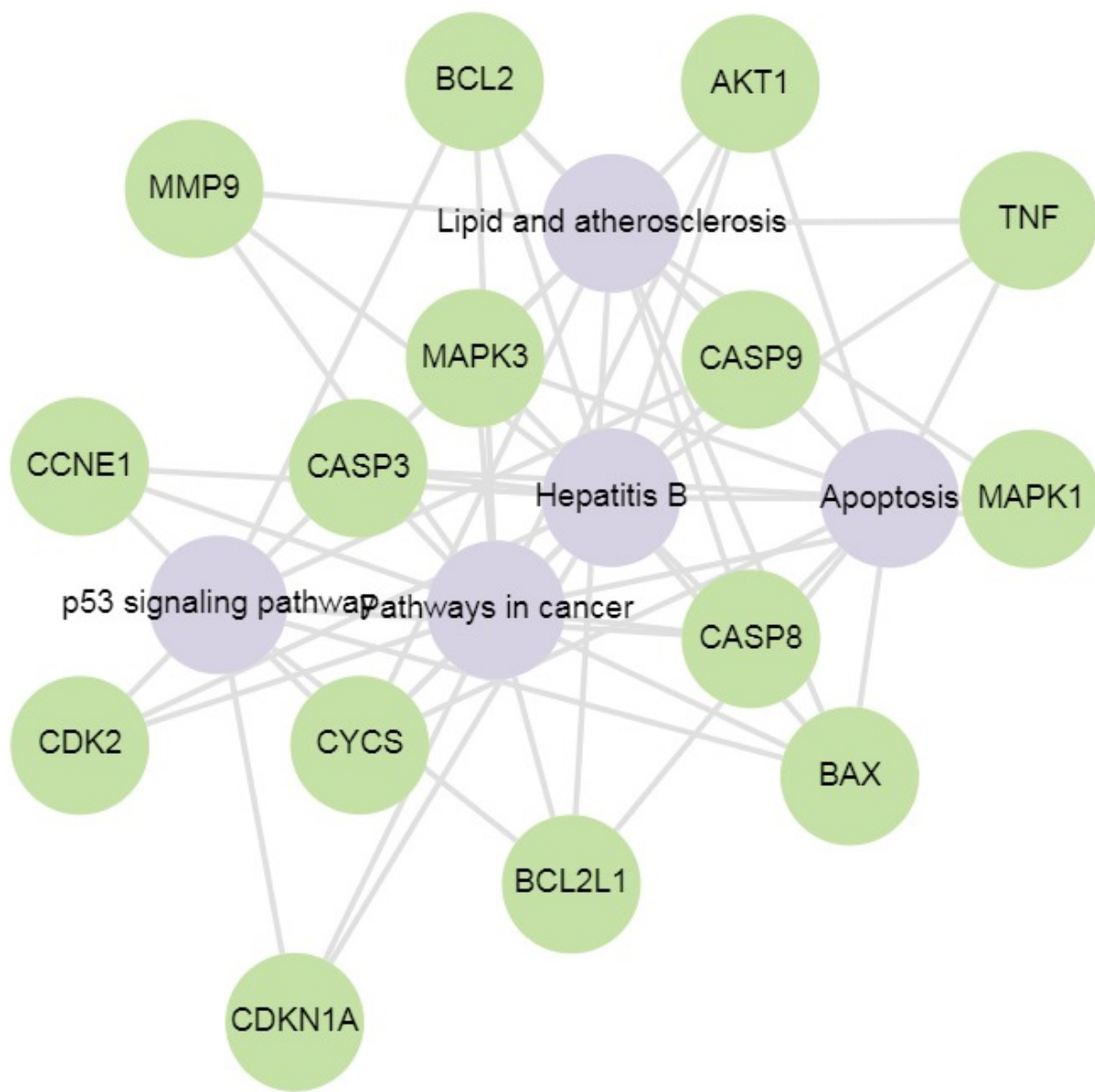


Figure 1

Gene–pathway interaction network of boswellic acid–related targets. Green nodes represent genes, and purple nodes indicate enriched biological pathways. The thickness of connections reflects the degree of functional association among genes and pathways.

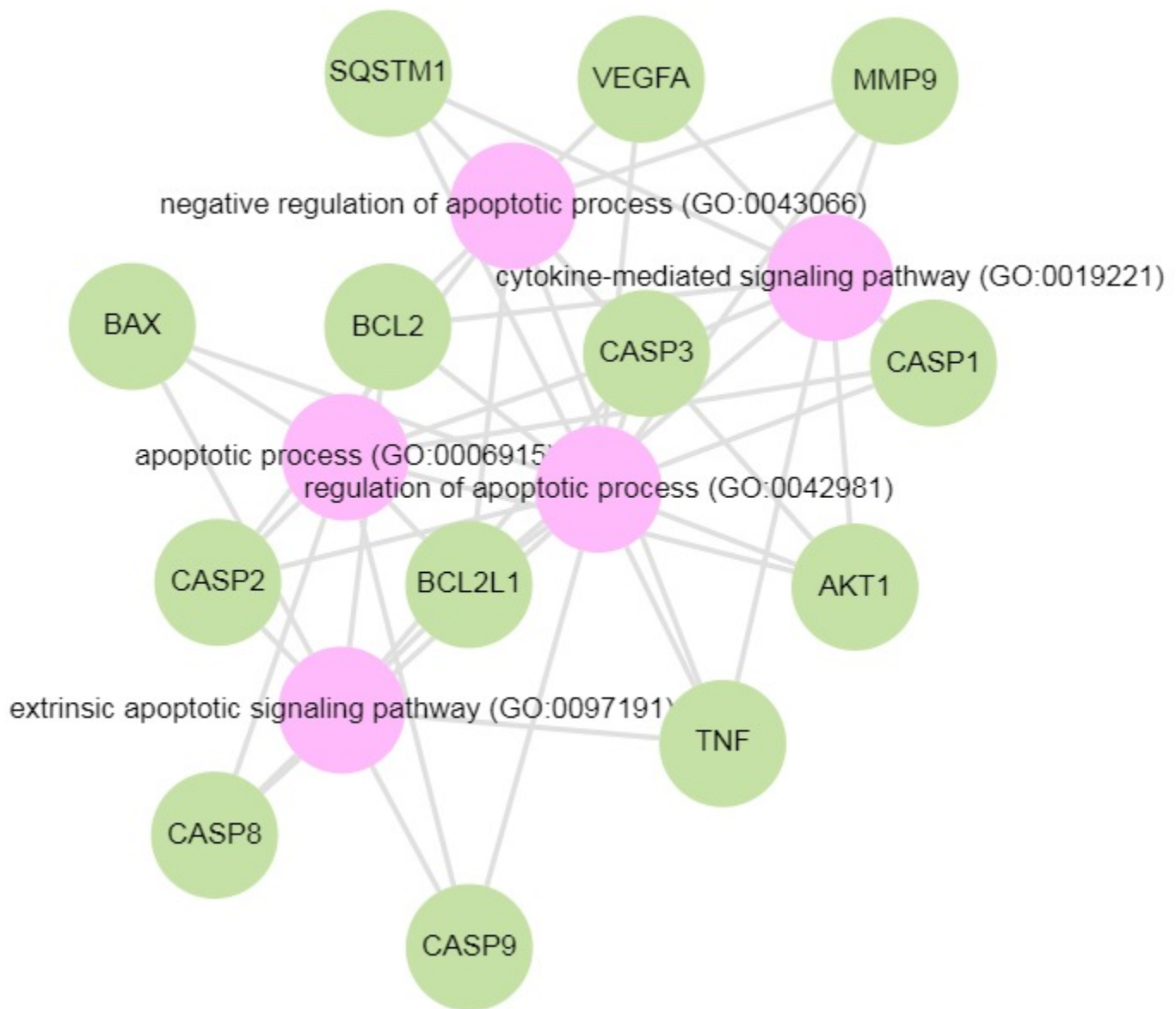


Figure 2

GO biological process network of boswellic acid-associated genes. Green nodes represent genes, and pink nodes represent enriched biological processes. The network highlights the strong enrichment of apoptotic and cytokine-mediated signaling pathways

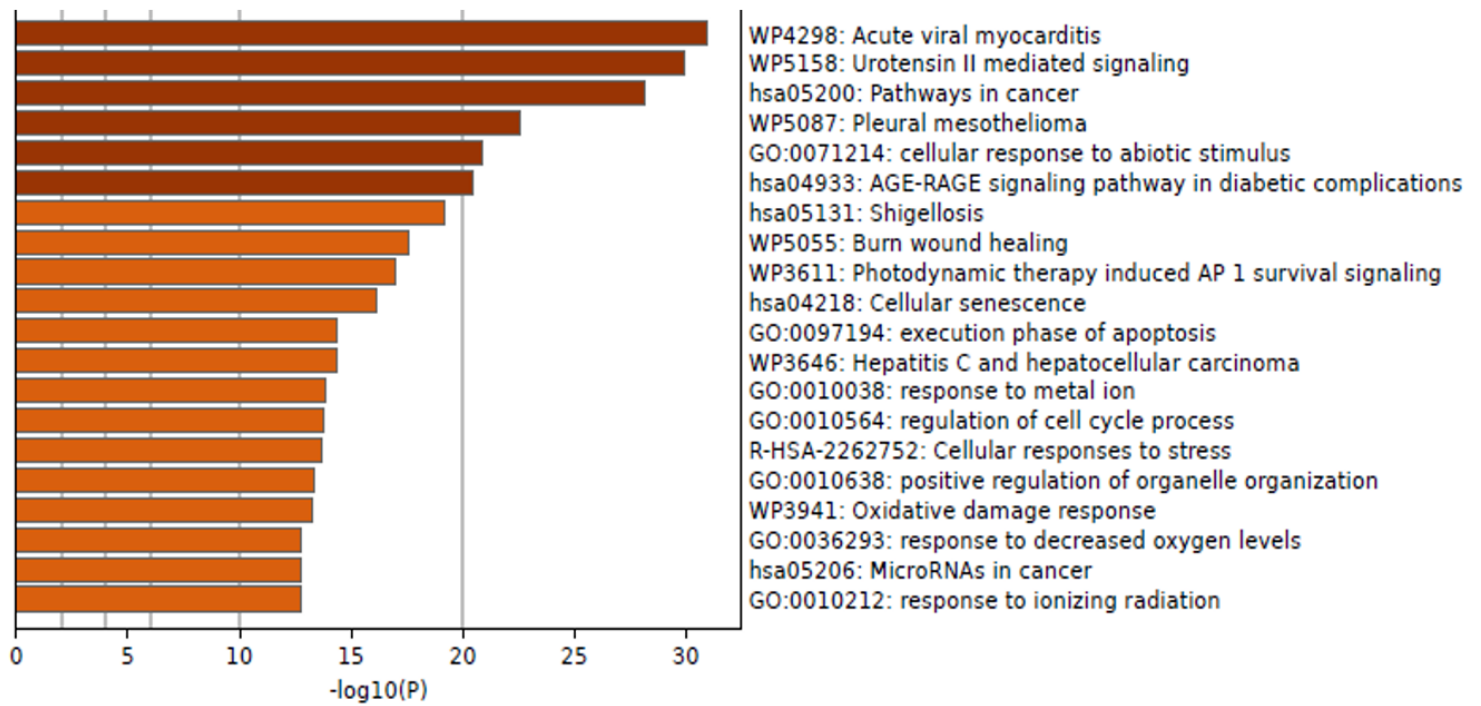


Figure 3

The heatmap shows significantly enriched biological pathways associated with Boswellia-responsive genes, highlighting key processes such as neuroinflammation, autophagy, oxidative stress, and neuronal survival.

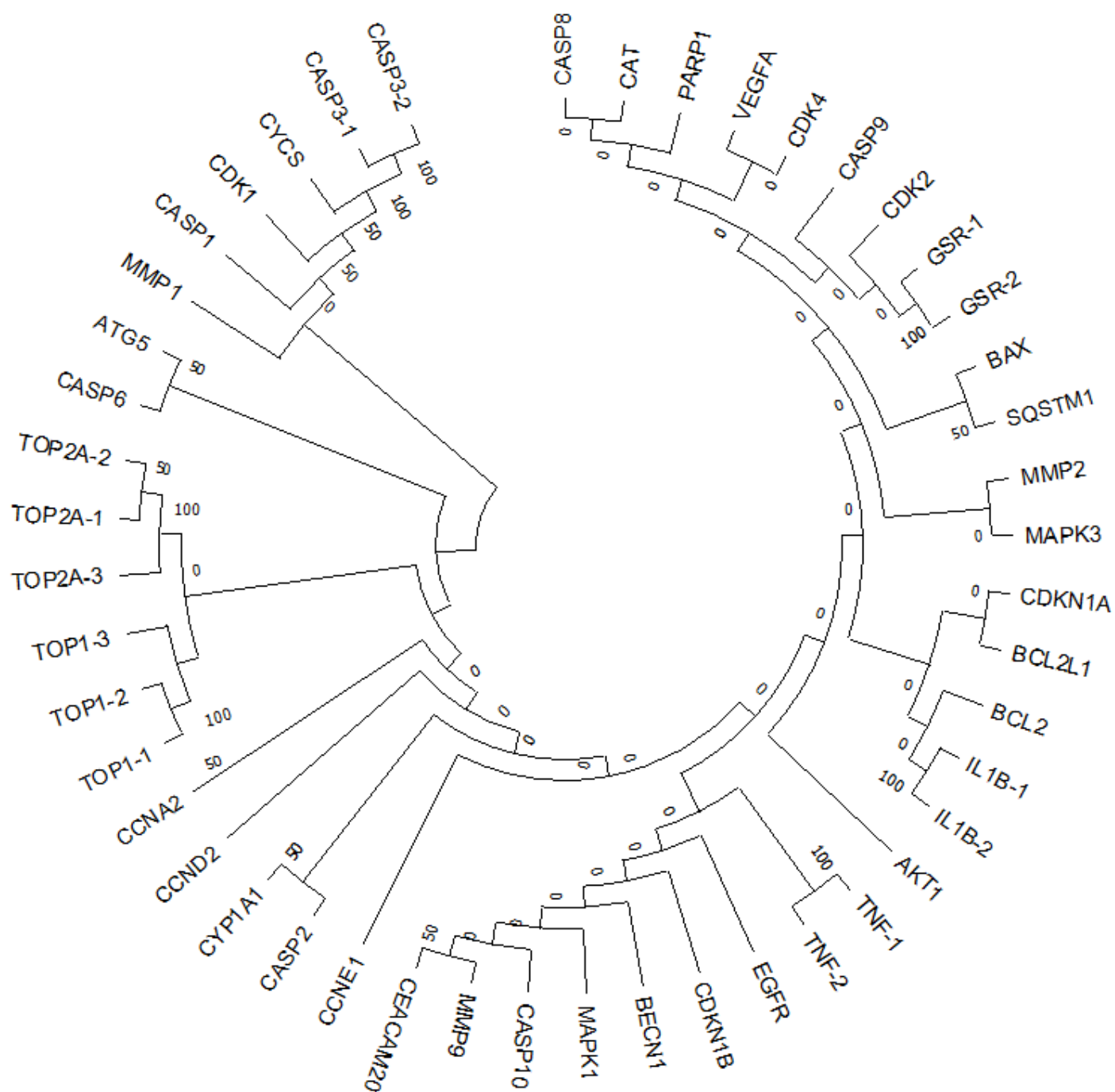


Figure 4

MEGA-based phylogenetic clustering of apoptosis, inflammation, oxidative stress, and autophagy-related genes, highlighting the multi-target network interactions of boswellic acids in Alzheimer's disease-related pathways.

Pathway diagram — Boswellic acids effects on Alzheimer's-related genes

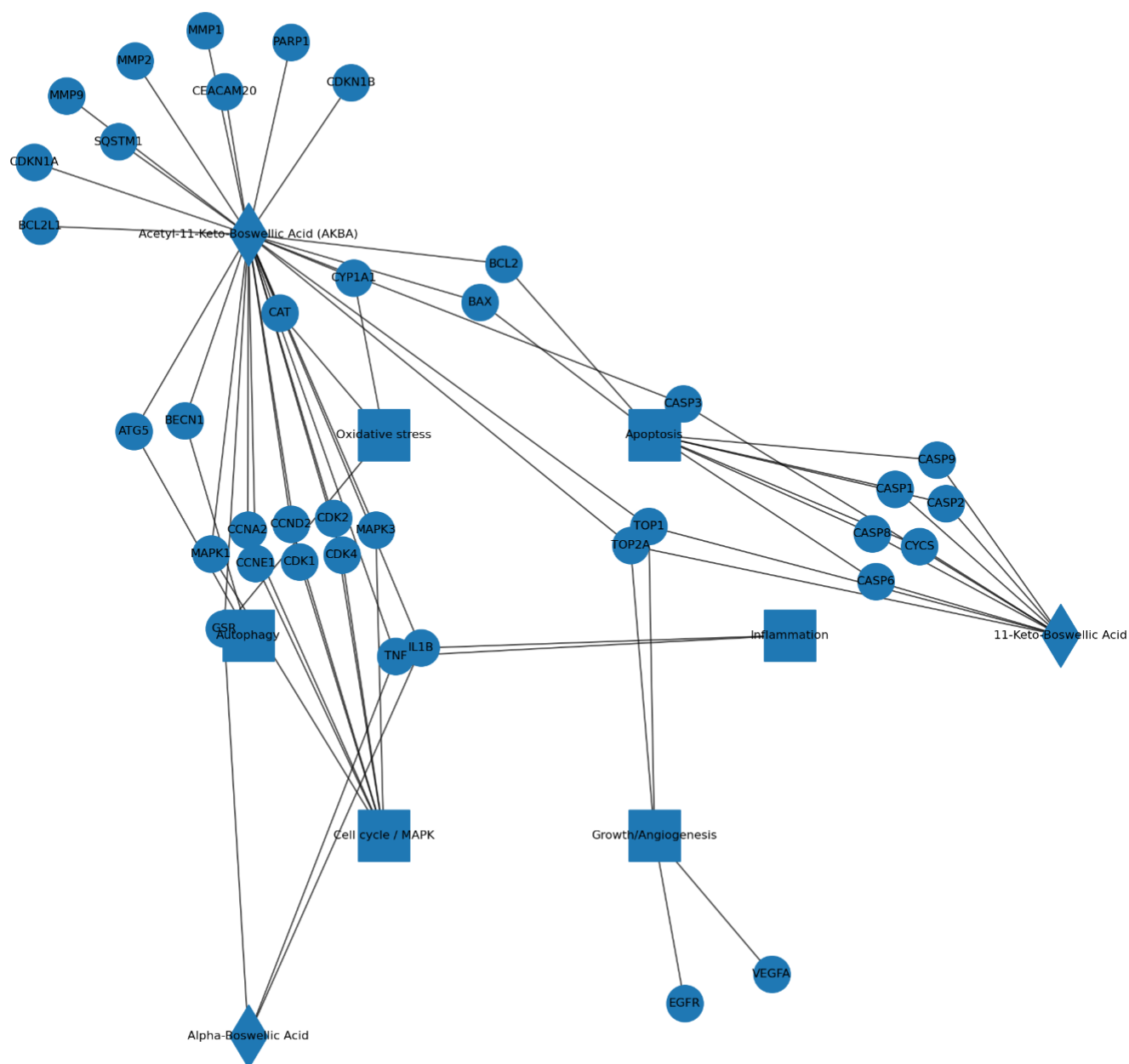


Figure 5

Network-based pathway map illustrating multi-pathway interactions of boswellic acid derivatives with Alzheimer's disease-related genes, highlighting their multi-target, non-linear regulatory effects across inflammation, apoptosis, oxidative stress, autophagy, and MAPK signaling pathways.