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REVIEW ARTICLE

# Natural bioactive compounds as notch signaling modulators: cutting-edge strategies for cancer therapy

**Hasna Bouhenni[1] · Mehrukh Zehravi[2] · Faruk Reza[3] · Sherouk Hussein Sweilam[4,5] · Uppuluri Varuna Naga Venkata Arjun[6] · Thukani Sathanantham Shanmugarajan[6] · Ponnammal Ganesan Mahesh[6] · Akiladevi Durairaj[6] · Patibandla Jahnavi[7] · Venkatesan Natarajan[8] · Ali G. Alkhathami[9] · Koula Doukani[1,10] · Talha Bin Emran[3]**

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## Abstract

Natural bioactive compounds have demonstrated potential in altering the Notch signaling system, a crucial regulator of cancer development. This review discusses the molecular interactions of various substances such as flavonoids, polyphenols, terpenoids, and alkaloids with ligands, receptors, and downstream effectors. Terpenoids like curcumin can combat Notch-mediated medication resistance, while flavonoids like quercetin prevent Notch receptor activation. Alkaloids that directly or indirectly modulate Notch signaling have anticancer effects. Preclinical and clinical investigations have demonstrated the effectiveness of several of these drugs, and several have progressed to clinical trials. The review emphasizes clinical trials to optimize the pharmacokinetics, safety, and therapeutic potential of natural medicines for cancer treatment. Natural bioactive substances targeting the Notch signaling system have the potential to develop cancer treatment. These treatments provide a potential alternative or supplement to current treatments due to their more targeted and less toxic approach to cancer cells. Natural bioactive compounds require further research to enhance pharmacokinetics, investigate processes, and conduct clinical trials.

Hasna Bouhenni and Mehrukh Zehravi have contributed equally to this work.

✉ Mehrukh Zehravi
mahrukh.zehravi@hotmail.com

✉ Koula Doukani
k_doukani@univ-tiaret.dz

✉ Talha Bin Emran
talhabmb@gmail.com

[1] Laboratory of AgroBiotechnology and Nutrition in Semi-Arid Zones, Faculty of Nature and Life Sciences, University of Ibn Khaldoun, Tiaret, Algeria

[2] Department of Clinical Pharmacy, College of Dentistry & Pharmacy, Buraydah Private Colleges, Buraydah 51418, Saudi Arabia

[3] Department of Pharmacy, Faculty of Health and Life Sciences, Daffodil International University, Dhaka 1216, Bangladesh

[4] Department of Pharmacognosy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia

[5] Department of Pharmacognosy, Faculty of Pharmacy, Egyptian Russian University, Cairo-Suez Road, Badr, Cairo 11829, Egypt

[6] Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), PV Vaithiyalingam Rd, Velan Nagar, Krishna Puram, Pallavaram, Chennai, Tamil Nadu 600117, India

[7] Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh, India

[8] School of Pharmacy, Sri Balaji Vidyapeeth (Deemed to Be University), Pondicherry 607402, India

[9] Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Khalid University, Abha, Saudi Arabia

[10] Laboratory of Animal Production Sciences and Techniques, Faculty of Nature and Life Sciences, University of Abdelhamid Ibn Badis, Mostaganem, Algeria

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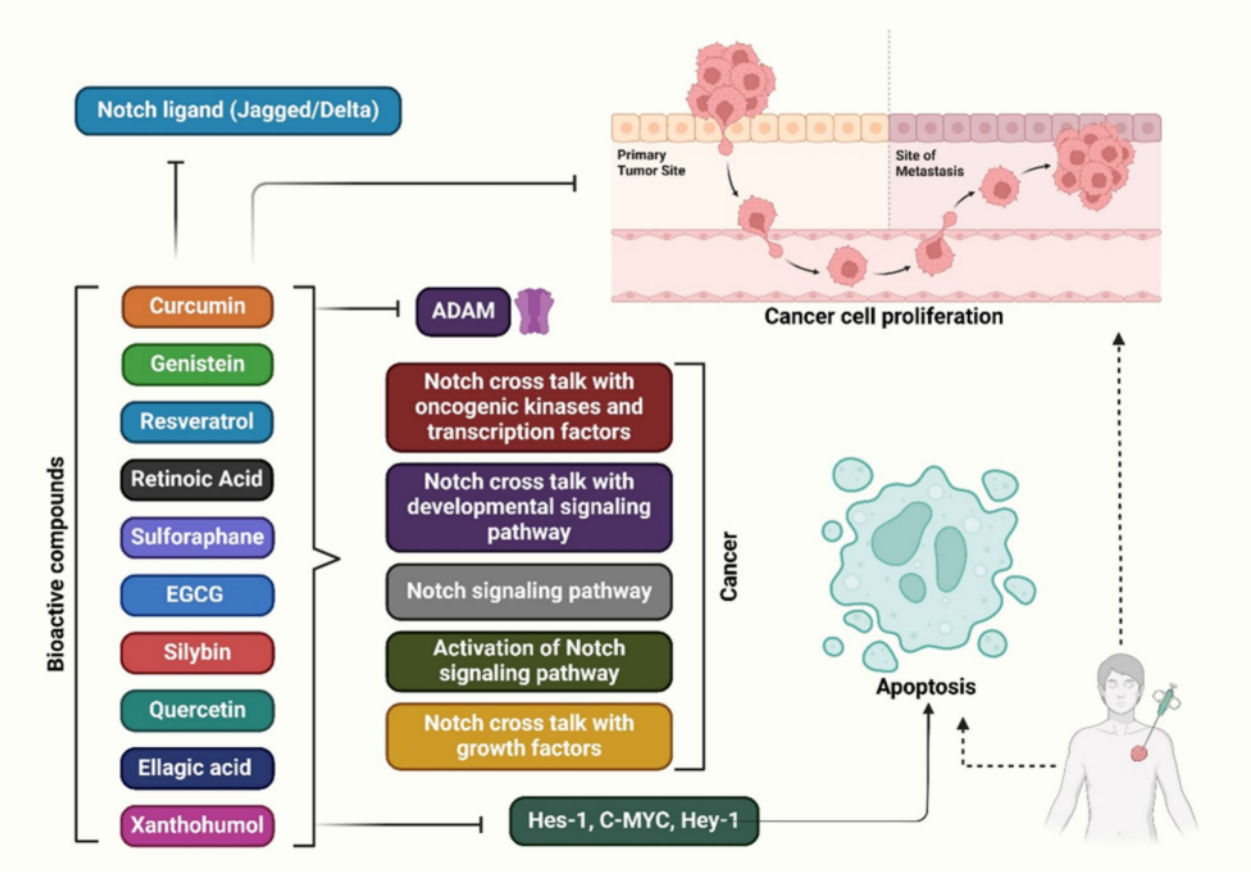
**Graphical Abstract**




**Keywords** Natural bioactive compounds · Cancer · Notch signaling pathway · Therapeutic strategies

## Introduction

Cancer has the highest clinical, social, and financial cost in terms of disability-adjusted life years. The top 15 cancer types globally are prostate, breast, and lung. Cancer ranks second globally in mortality (8.97 million deaths) after ischemic heart disease, but is expected to overtake it as the leading cause of death in 2060 [1]. Colorectal cancer, the second most frequent cancer and the third leading cause of cancer-related deaths globally, saw 1.8 million new cases and 881,000 deaths [2]. Breast cancer is the most prevalent malignant tumor in women globally, affecting 36% of cancer patients and an estimated 2.089 million women [3–5]. Cancer is an extremely harmful disease that seriously risks human health [6]. Among the available treatment options are immunotherapy, targeted therapy, chemotherapy, radiation, and surgery [7]. The disease's poor prognosis, severe side effects, drug resistance, and high recurrence rates necessitate novel treatments or targets, with Notch being a prime molecular target [8]. Notch signaling (Fig. 1) is a crucial pathway linked to various human malignancies, including glioblastoma, breast, colorectal, lung, pancreatic, and prostate cancers [9]. It is essential for several biological functions, including differentiation, cell division, and cancer stem cell maintenance [10]. In several cancer types, clinical studies show a negative relationship between Notch expression and patient survival, suggesting that higher Notch activation is linked to more aggressive malignancy. The alteration of the expression levels of the Notch pathway may serve as a potential therapeutic approach for cancer treatment [11]. Jagged1 (JAG1), a Notch ligand, initiates Notch signaling, causing poor clinical prognosis in various cancer types. It regulates oncogenic processes and activates factors such as angiogenesis, drug resistance, metastasis, and proliferation, making JAG1 a popular cancer therapy target [12]. Notch-1 activation is more likely to cause aggressive production of functional and phenotypic alterations in cancer cells associated with mesenchymal transition than other Notch receptors. Direct control of Slug and Snail leads to alterations in E-Cadherin and other mesenchymal markers,

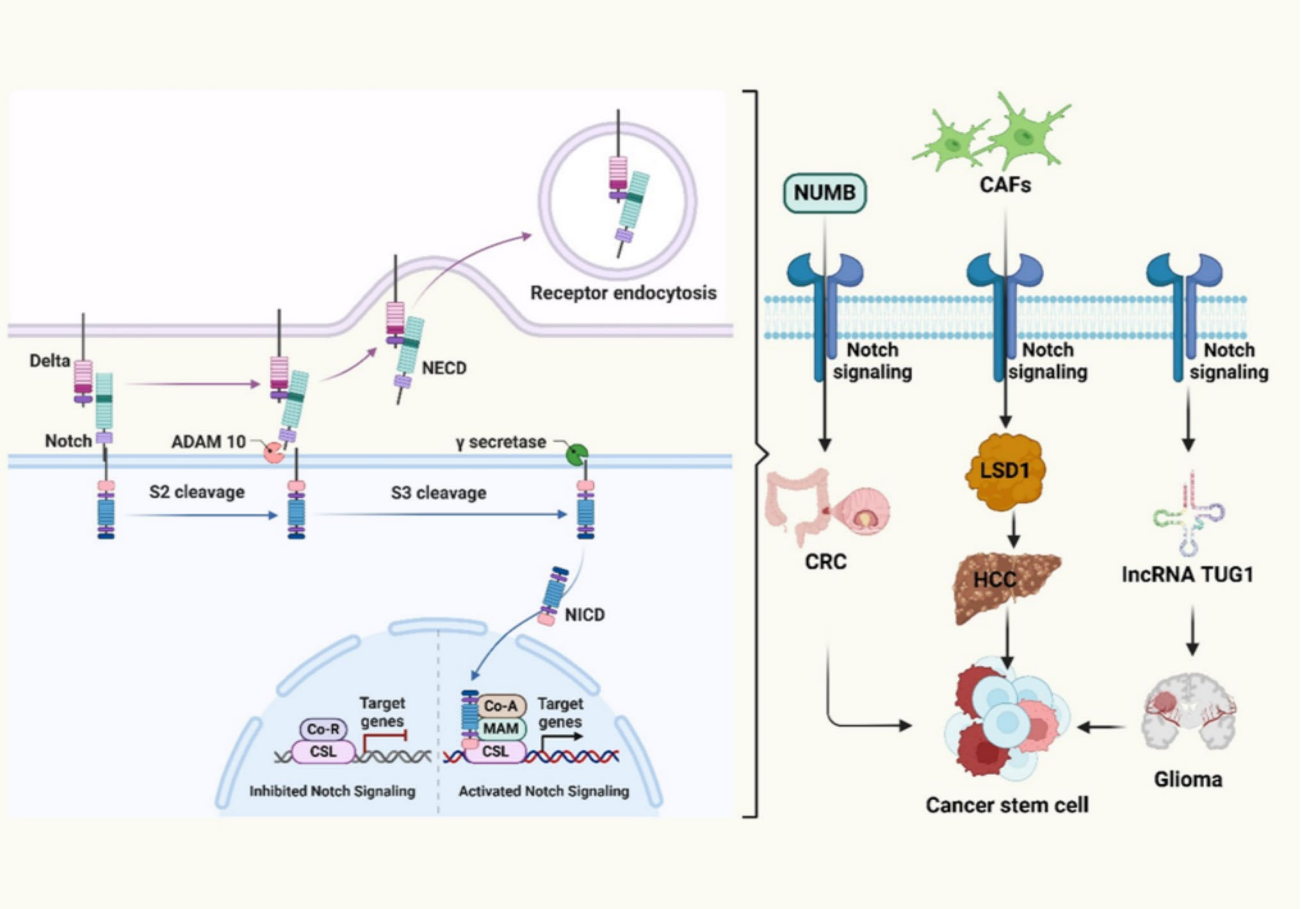



**Fig. 1** The Notch signaling pathway is a crucial cell signaling system that regulates cell fate, differentiation, proliferation, and death, potentially acting as a tumor suppressor or oncogene in cancer progression

ultimately resulting in EMT. Furthermore, Jagged1 ligand-mediated Notch-1 activation in epithelial cells induces a similar mesenchymal transition, highlighting the importance of Jagged1-mediated Notch-1 signaling activation in EMT development [13].

Natural bioactive compounds blocking Notch are considered the best therapeutic agents due to their low toxicity, high therapeutic index, and improved bioavailability potential. Small-molecule inhibitors with Notch-inhibiting activity may be utilized to treat solid tumors and cancer stem cells (CSCs). These inhibitors are derived from compounds like isoflavone genistein [14] found in soy products; sulforaphane is derived from broccoli [15]. Quercetin is found in many fruits and vegetables [16]. Curcumin is used as a flavoring agent [16]; and resveratrol is found in grapes [17], peanuts, and some berries. Verrucarin J was demonstrated to effectively inhibit the Notch-1-mediated transition from epithelial to mesenchymal in metastatic colon cancer [18]. Withaferin A (WA) is a medication that inhibits the transcriptional activity of STAT3, a key transcription factor in colon cancer cells [19]. WA has a chemopreventive effect in models of spontaneous and inflammation-associated colon carcinogenesis. It inhibited the expression of pro-survival and inflammatory markers in APCMin/ + and AOM/DSS models [20]. Psoralidin inhibits Notch-1-mediated EMT activation in ALDH + and ALDH-negative breast cancer tumors [21]. The review highlights that natural bioactive compounds exhibit potent anticancer properties by altering the Notch signaling system, promoting apoptosis, reducing metastasis, and chemosensitizing in cancerous cells. It also demonstrates the potential of natural bioactive compounds as modulators of the Notch signaling pathway, highlighting their potential in innovative and less toxic cancer therapy approaches.

## Notch signaling pathway

Notch signaling initiates when Notch ligands directly interact with receptors found on various cells. Notch ligands trigger one of four membrane-bound Notch receptors: Notch-1, -2, -3, and -4. ADAM-10 cleaves Notch receptor

S2 during ligand–receptor interaction, releasing the NECD, which is then endocytosed into the ligand-expressing cell [22–24]. Additionally, ligand-independent pathways can activate Notch [25]. S2 cleavage is preferentially carried out by ADAM-17 in ligand-independent circumstances [26]. After Notch is cleaved by ADAM-10 or ADAM-17, the gamma-secretase complex cleaves Notch S3/S4 [27]. Gamma-secretase cleavage (NICD) releases the Notch intracellular domain, which binds the transcription factor CSL in mammals, represented by CBF-1/RBPJ-κ [22]. The transcriptional activation complex and mastermind-like protein (MAML) are activated when NICD attaches to RBP-Jκ, thereby triggering transcription [24, 28]. Tumor recurrence and eventual patient relapse are made possible by the survival of CSCs after therapy [29]. Accordingly, sphere formation in cancer cells is either inhibited or enhanced by Notch knockdown or overexpression [30, 31]. The notch pathway (Fig. 2) interacts with NF-κB, Ras, Wnt, and JAK/STAT pathways, supporting cancer cell growth and regulating CSCs and EMT [32]. A cooperative interaction between the pathways is shown by the fact that HMLE human mammary epithelial cells underwent malignant transformation when Ras and Notch-1 were overexpressed simultaneously, although neither gene alone caused the transformation [33]. The Wnt signaling pathways (Fig. 2) transcriptional target is the Notch ligand Jagged1 [34]. Mouse embryonic fibroblasts display increased Hes1 reporter activity when β-catenin is overexpressed, and NICD in HEK293 human embryonic kidney cells may be bound by β-catenin, a Wnt signaling cascade [35]. Wnt stimulation can increase the activity of the Notch pathway. JAK/STAT signaling and NF-κB both have bidirectional crosstalk with Notch [36]. Since NF-κB is a Notch target gene [37], deactivation of the NF-κB pathway may also occur as a result of Notch suppression. Furthermore, Notch controls angiogenesis in cancerous cells [37]. Cell type and environment have an impact on how notch signaling controls gene expression [9, 24, 37].

Depending on the biological environment, notch has been demonstrated to have both a tumor-suppressive and an oncogenic function in certain cancer cells [9, 38]. Notch mutations can either activate or inactivate in response to the overall activity of Notch as an oncogene or tumor suppressor in a specific cellular setting [38]. Research is underway to modify Notch signaling in cancer through various methods, such as the use of gamma-secretase inhibitors (GSIs) and monoclonal antibodies [38, 39]. Despite occasionally being

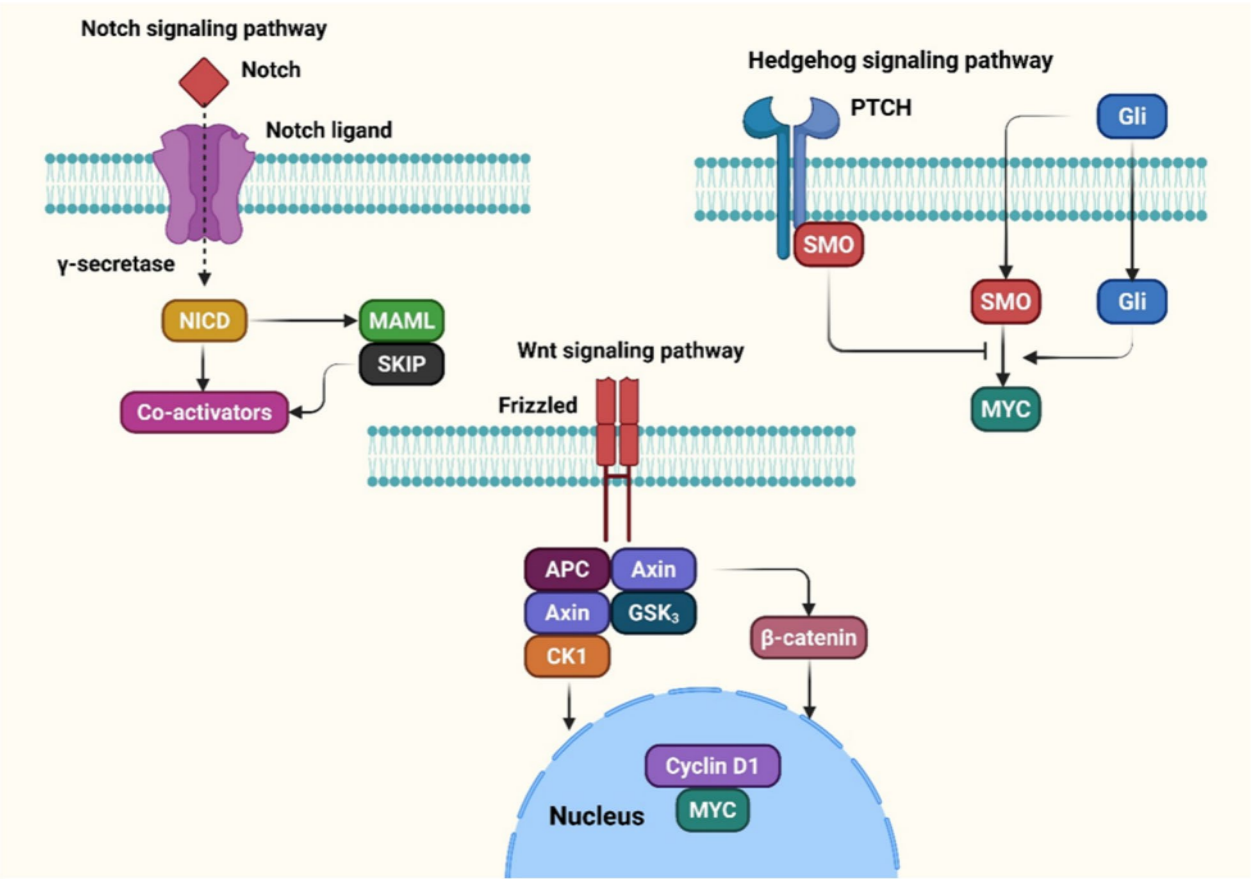



**Fig. 2** Illustration of Notch, Wnt, and Hedgehog signaling pathways

effective in tumor remission, GSI usage in cancer is linked to unfavorable side effects as nausea, vomiting, and diarrhea [39, 40]. The Notch signaling pathway in mammals is triggered by the interaction between Notch [41–44] and its membrane-bound ligands, Jagged1, Jagged2, and δ-like ligands 1, 3, and 4 [45]. The DSL (Delta/Serrate/Lag2) amino-terminal domain is the substrate for various epidermal growth factor-like domains [46], which is a characteristic shared by these ligands. Furin-like convertase, a mature enzyme with two non-covalently connected subunits, breaks down precursor protein for notch receptors, which is glycosylated by the Golgi apparatus before being sent to the cell surface [47]. The Notch receptor, located on the intracellular membrane, is crucial for signal transduction. Its extracellular portion has a cysteine-rich repeat domain. TACE cleaves the receptor, releasing the extracellular component. The NICD is released into the cytoplasm [48]. NICD can be transferred to the nucleus to recruit coactivator nuclear proteins like CBP/p300 and MAML1-3, heterodimerizing with C promoter-binding factor (CBP) linked to core co-repressor proteins [49, 50]. CBP, when associated with NICD, transforms from a transcriptional repressor to an activator, targeting genes like p21 CIP1, cyclin D1, Hes1, Hey1, NF-κB, and c-Myc [51–54]. This signaling pathway is crucial for the proliferation and differentiation of stem cells, ensuring their maintenance and growth [55]. Higher Notch activation in CSCs has been related to strong tumorigenicity, resistance to chemotherapeutic drugs, and the capacity to generate tumor spheres [56]. The EMT phenotype is crucial for the proliferation and clonogenic capability of the pancreatic cancer cell line, AsPC-1, the increase in mesenchymal cell markers like Zinc finger E-box-binding homeobox 1,2 (ZEB1, ZEB2), SNAIL2, and vimentin, and the decrease in epithelial cell markers like E-cadherin [57].

### Ligand–receptor interaction

The affinity between Notch and Delta and Serrate ligands is higher than homotypic interactions between Delta molecules. This contradicts previous hypotheses, as Serrate and Notch have similar affinity. Fringe does not affect the Notch pathway's ligand–receptor interactions in cultured cells. Serrate is a transmembrane ligand that can participate in reciprocal trans-endocytosis, similar to Delta [58]. A missense mutant of the Notch ligand Jagged1 (Nodder, Ndr) maintained a cellular distribution similar to wild-type Jagged1 without interaction with Notch receptors. The E3 ubiquitin ligase Mind bomb interacts with both Jagged1WT and Jagged1Ndr, but Jagged1WT exhibited increased ubiquitylation after co-cultivation with Notch receptor-expressing cells. The interaction-dead Jagged1Ndr ligand offers new insights into receptor–ligand interaction in Notch ligand intracellular trafficking [59]. Understanding Notch signaling in cancer and immunological diseases is crucial. Despite numerous drugs, challenges like off-target effects and therapy-related toxicities persist. The study focuses on ligand-specific control of immune responses and suggests clinical use of ligand-derived drugs [60]. The Notch signaling pathway uses ligands and receptors to send messages to neighboring cells. Fringe glycosyltransferases regulate these interactions. A study characterized trans-activation, cis-inhibition, and cis-activation signaling efficiencies in Chinese hamster and mouse cell lines. All four ligands bind receptors in both cis and trans, and all ligands trans-activate both receptors. Cis-interactions were primarily inhibitory, with Lfng decreasing Jagged-mediated trans-activation and enhancing Delta-mediated trans-activation. The map of receptor–ligand–Fringe interaction results should guide logical Notch pathway perturbation and regulation [61].

## Natural bioactive compounds targeting Notch signaling pathways

Research and exploration of medicines targeting the Notch pathway have been extensively conducted to treat various disorders. Notch receptor inhibitors effectively stop Notch signaling and downstream gene activation by blocking transmembrane cleavage and releasing NICDs into the cytoplasm. The study found that DAPT, a γ-secretase inhibitor, effectively inhibited cisplatin-resistant osteosarcoma, with its anticancer effect being more potent when used in combination with cisplatin [62]. This inhibitor is widely recognized as a potential therapeutic approach for Alzheimer's disease. Alzheimer's disease is characterized by the formation of β-amyloid plaques, which are formed when γ-secretase proteolyzes the amyloid precursor protein. Two common GSIs, semagacestat and avagacestat, demonstrated potency against C99 and Notch amyloid precursor proteins, with γ-secretase modulators enhancing their effectiveness in combination [63]. Verteporfifin, a photosensitizer, is a substrate-selective γ-secretase inhibitor that binds specifically to APP C99 but not Notch-1 [64]. However, research on the severe side effects of blocking Notch, which result in a recurrence in presenilin1, is extensive, suggesting that blocking Notch is a bad therapeutic strategy [65]; therefore, the effectiveness and safety are still unknown. GSIs have been shown to cause tumor cell death when used to treat multiple myeloma, and when paired with bortezomib, they both individually and synergistically suppressed Notch signaling [66]. GSI-XII is cytotoxic when the Notch pathway is inhibited, and the effectiveness is increased when the proteasome inhibitory activity is diminished [66]. Notch receptor silencing is an unpredictable and potentially harmful treatment strategy due to its lack of specificity. The balance between Notch and other pathways like PI3K/Akt, NFκB, and STAT3 remains

unclear [67]. A study investigates suppressing Notch receptors for high-specificity antibodies, drug conjugates, and targeted DLL 3 therapies, revealing partial effectiveness in response rate, overall survival, and progression-free survival [68]. Despite resolving the specificity issue, antibodies and synthetic drugs still face the same problem as GSIs: a lack of understanding of pathways and one-size-fits-all inhibitory action. The genesis and progression of tumors are influenced by interactions between miRNAs and the Notch signaling system [69, 70]. Therefore, it is anticipated that miRNA modulators will be attractive candidates for balancing Notch signaling. MiR-1275 had a promoter function in lung adenocarcinoma by activating Notch, which was discovered to be closely linked to maintaining cell stemness. When miR-1275 was turned down, the impact diminished [71]. High-level systemic sclerosis is associated with a scaffold-long noncoding RNA called HOTAIR [72]. Notch-1 expression is inhibited by HOTAIR's methylation of miRNA-34a, which is regulated by the histone methyltransferase EZH2 [72]. However, there are currently no appropriate medicines that target miRNAs because of the intricate networks of miRNAs and Notch signaling [73]. GSI-resistant malignancy, caused by abnormal mutations in the Notch gene, and other Notch-dependent human cancer cell lines, including primary human T-cell acute lymphoblastic leukemia, effectively respond to it [73]. Natural compounds possess anti-proliferative, proapoptotic, anti-metastatic, and anti-angiogenic properties, as well as the ability to regulate autophagy and enhance treatment resistance. They possess immunity-modulating, anti-inflammatory, anti-fibrotic, and anticancer properties [74–77]. It should come as no surprise that they have been widely used for thousands of years as common dietary adjuvants in the healthcare sector [76, 78]. Natural products' promise for clinical therapies has not been fully realized due to declining public interest and increased pressure on pharmaceutical companies to explore their potential [79, 80]. The lack of funds is one of the causes. The industry's predicted earnings have declined due to rising costs, such as litigation, competitive marketing, and safety regulations, leading to a significant loss of capital [80].

## Bioactive compounds treated cancers by modulating the Notch pathway

### Bioactive compounds suppressed the Notch signaling pathway's activation

Notch receptors' extracellular domain binds to ligands, typically found on the surface of nearby signal-sending cells [81], to begin Notch. In both non-cancerous and malignant disorders, cell fate and proliferation are regulated by the Notch signaling system [10].

#### Epigallocatechin-3-gallate

One of the most popular drinks in the world, especially in Asia, is tea. Green tea is widely known to have several health advantages, most of which may be attributed to its primary bioactive component, which is known as EGCG [82]. EGCG has anti-inflammatory and anticancer effects and is a potent antioxidant [82–84]. EGCG (Fig. 3) can treat various cancers by altering signaling pathways like ERK1/2, NF-κB, Notch, and Akt [84–87]. Additionally, EGCG demonstrated potent effects in reducing carcinogenesis in mice with lip and tongue cancer due to K-Ras mutations [88]. Moreover, EGCG was found to have a molecular effect on the activity of the Notch signaling pathway. EGCG's blood circulation concentrations in mice were low, with concentrations of $0.703 \pm 0.057$ µg/mL 1 h after injection and $0.239 \pm 0.057$ µg/mL after 2 h, even at 25 mg/kg body weight. The study suggests that 800 mg of the medication is required daily to achieve a similar circulation concentration in people when taken orally [88]. EGCG significantly increases drug resistance to doxorubicin by inactivating Notch 3 and DLL 3, which target LncRNA SOX2OT variant 7, through autophagy and stemness inhibition. The Lv-Notch-3 lentivirus, which knocks down Notch-3, significantly reduces tumor growth and cancer marker expression [89]. Furthermore, EGCG's oxides have a larger capacity to control Notch signaling due to their high oxidizability and instability and the purity of the oxide [90]. EGCG effectively inhibited Notch-1 in various cancer cell lines, including colon cancer, neuroblastoma, and cholangiocarcinoma [91–94]. In addition, EGCG therapy altered Notch-4 expression in tongue squamous cell carcinoma cell lines, with the effect's direction varying based on cell type and EGCG incubation duration [95]. In neuroblastoma cells, EGCG inhibited MMP-2 and -9 and produced E-cadherin [92]. The addition of cisplatin enhanced the reduction in sphere formation in head and neck cancer cells caused by EGCG-mediated Notch inhibition [91]. Additionally, cisplatin, either alone or in conjunction with EGCG, pre-treated head and neck CSCs before transplantation into BALB/c nude mice suppressed tumor development in both models, with co-treatment having the highest impact [91]. EGCG was found to prevent tumoral lesions on the tongue and lip in K-Ras transgenic mice by downregulating the Notch pathway [88]. Moreover, EGCG decreases the expression of Notch receptors, including Notch-1 [90–92, 96] and Notch-2 [97]. EGCG effectively suppressed the activation of Notch in tongue cancer mice by decreasing Notch-1 expression, leading to cell death and hindering proliferation [88]. Furthermore, EGCG also encourages Notch-1 suppression and cleavage in 5-Fluorouracil-resistant cell lines [94], indicating that EGCG overcomes 5-Fluorouracil resistance via modifying Notch activity.

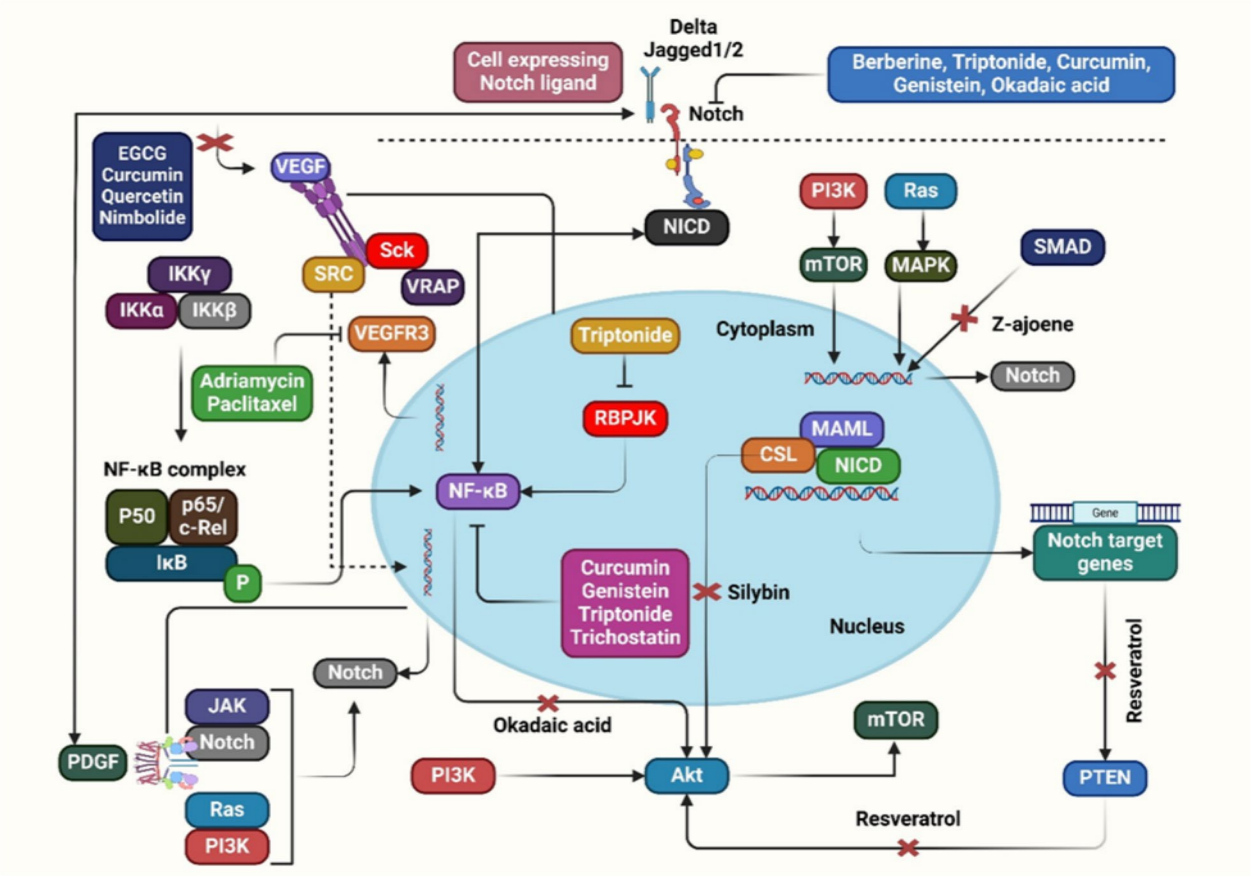



**Fig. 3** EGCG's ability to alter Notch signaling pathways, crucial for cell fate, proliferation, differentiation, and apoptosis, has garnered significant interest in cancer treatment

## Resveratrol

Resveratrol, a compound with the chemical formula 3,4',5-trihydroxy-trans-stilbene, is likely to improve cancer treatment [98]. Research on resveratrol, a stilbene found in blueberries, peanuts, and grapes, reveals that Notch signaling is context dependent and can be both tumor suppressive and oncogenic in cancer cells. There is growing evidence that Notch activation is essential for tumor suppression in several cancer types, such as brain and neuroendocrine tumors [99, 100]. Resveratrol treatment in neuroendocrine cancer cells activates Notch signaling, suppresses Notch-2 expression, and ASCL-1 decreases carcinoid growth and inhibits neuroendocrine hormone production [101]. Additionally, resveratrol has been found to induce apoptosis, increase Notch-2 mRNA, and decrease the neuroendocrine marker ASCL-1 in medullary thyroid cancer [102]. Resveratrol inhibited the growth of ATC cells in vitro and in vivo by activating Notch-1 signaling [103]. The combined findings support the notion of Notch's tumor-suppressive function in both MTC and ATC [102, 103]. Resveratrol stimulation of Notch-1 and Notch-2 in medulloblastoma cells did not significantly impact their development [104]. Moreover, resveratrol was found to inhibit Notch in various cancer cell cultures, including T-ALL, cervical, ovarian, and breast cancer [17, 105–107]. GSI-cultivated ovarian and cervical cancer cells showed decreased Hes1 protein expression but maintained viability [105, 106]. The downregulation of Notch receptors and ligands, including Notch-1, Notch-2, Notch-4, DLL1, DLL4, and Jagged1, can effectively inhibit cell cycle and proliferation [101, 103, 105], promote apoptosis and redifferentiation [103], stop tumor recurrence [108], and obstruct autophagy [109] in cancer. However, considering its limited significance to resveratrol-induced differentiation and death, Notch signaling may not be uniformly essential in human medulloblastoma cells [110]. Autophagy was more successfully blocked when a Notch inhibitor and resveratrol were used together, indicating that this combination may be used as a cancer treatment [109]. The combination of resveratrol and the γ-secretase inhibitor RO4929097 has been shown to effectively suppress Glioblastoma, a disease with poor prognosis and treatment resistance. This inhibitor effectively inhibits Notch signaling by significantly reducing CDK4, leading to impaired lysosomal function and

autophagy post-apoptosis [109]. A study found that resveratrol suppresses MAML2, a Notch target gene coactivator, leading to reduced binding of the OCT1 transcription factor and increased occupancy of DNMT3B [111]. Resveratrol effectively prevented anaplastic thyroid cancer in HTh7 and 8505C cells. Elevated expression of TTF1, TTF2, Pax8, and NIS indicates Notch pathway activation, leading to S cell cycle arrest, apoptosis, and enhanced cancer cell redifferentiation [103]. Research indicates that increasing resveratrol doses decreases Notch protein expression and significantly impacts apoptotic pathways controlled by PI3K/Akt and p53, suggesting improved treatment [17].

## Curcumin

Curcumin, a spice found in *Curcuma longa* rhizomes, is a key component in various cuisines, providing distinct flavors in mustards and curries [112]. Curcumin has been recognized and recommended in traditional medicine for its antibiotic, wound-healing, anti-inflammatory, and anticancer properties [113–118]. However, curcumin's potential as a medication is limited by its poor intestinal absorption, low bioavailability, low solubility in aqueous solutions, and pharmacokinetic properties [117]. Curcumin (Fig. 4) decreases the levels of Notch-1 [119–123], Notch-3 [123], and Jagged1 [124], which prevents cellular self-renewal, apoptosis [119, 125], motility, migration, and invasion and results in DNA-mediated cell death. Significantly, curcumin may downregulate paralogous proteins, gamma-secretase protein complex, and miR-27a [126], while upregulating miR222-3p [127] and miR-34a [128]. In human osteosarcoma U2OS cells, curcumin therapy inhibited invasion; this effect was reversed by overexpressing Notch-1 [129], suggesting that Notch-1 mediates curcumin's anticancer action. Curcumin inhibited the ability of cleaved Notch-1 to bind DNA in human prostate DU145 cells, but it did not affect Notch-1 expression [130]. Due to turmeric's low bioavailability of curcumin in its dietary supply, it is recommended to use curcumin analogs or improved delivery methods [131]. A study found that oral treatment of Meriva®, a turmeric/phospholipid formulation, combined with oxaliplatin therapy effectively inhibited NICD-1 in tumor tissue in a xenograft mouse model [125], suggesting that curcumin might improve anticancer drugs. Curcumin regulates Notch-related pathways and activities by

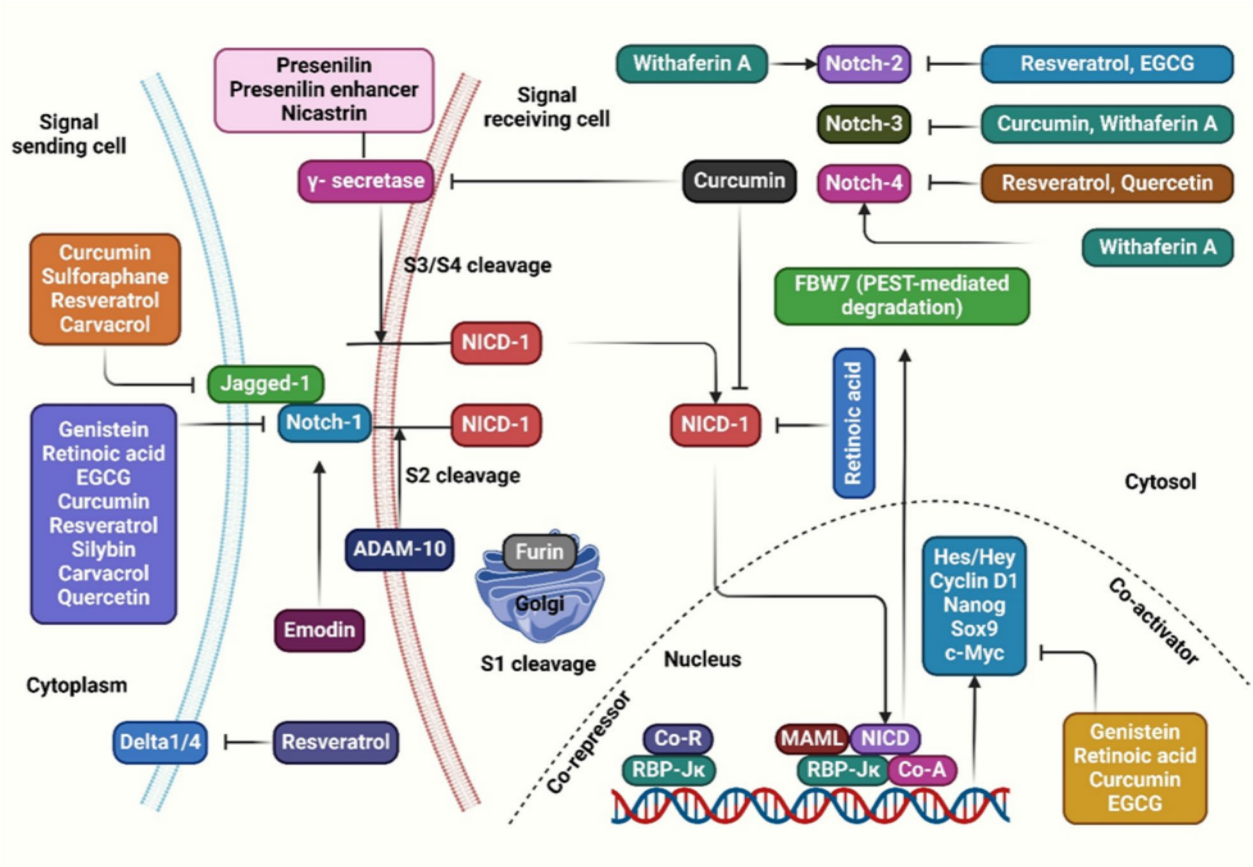



**Fig. 4** Curcumin's strong anticancer potential is due to its ability to modulate the Notch signaling system, a common dysregulation in various cancer types

suppressing MMP-2, -9, and Notch-1 expression in U2OS osteosarcoma cells [132]. Crucially, curcumin administration also prevents invasion in U2OS cells, and Notch-1 overexpression restores invasion [132]. Curcumin significantly reduces Hes1 in DU145 cells treated with NICD, indicating its DNA-binding capacity, rather than influencing Notch cleavage [130]. Additionally, curcumin inhibits the Notch-1 pathway in DU 145 cells, causing cycle arrest and suppressing Bcl-2 expression [129]. Curcumin intervention led to higher apoptosis levels in Notch-1-silenced DU 145 cells, indicating the need for further research to identify undiscovered genes collaborating with Notch [129]. The anticancer medication promoted Notch 3-responsive genes in myeloma P3 × 63Ag8 cells, inhibited Bcl-2, and increased p53 expression, with noticeable effects at doses exceeding 30 μM [133]. Moreover, curcumin may also target MMP-2. Curcumin, with an $IC_{50}$ of 0.25 mg/ml, inhibited SOX10, Notch-1, and Hes1 expression in melanoma cell lines A375 and HT 144, increasing miR-222-3p expression [127]. A nine-week-old nude boy was used as a xenograft model, and BALB/c mice showed stronger evidence after receiving luteolin and curcumin in combination [134].

### Genistein

Genistein, an isoflavone, was first discovered in Dyer's *Genista tinctoria* L., a brooming plant, and is widely found in the Fabaceae family [135]. It is an isoflavone generated from soy that is polyphenolic. Genistein supplementation showed lower Notch-2 mRNA levels in mammary epithelial cells compared to those fed casein [136]. Genistein was found to suppress Notch-1 protein expression in various cancer cell lines, including neuroblastoma, colon, and breast cancer [137–139]. Additionally, genistein reduced invasion-related gene mRNA expression in HT-29 cells, partially reversed EMT, and promoted apoptosis by suppressing the NF-κB and Notch-1 pathways and increasing the expression of caspase-3 and Bax/Bcl-2 [138]. Genome-wide DNA methylation arrays and gene enrichment studies have identified specific gene targets for prostate cancer treatment [140]. Gene expression profile studies reveal limited post-transcriptional mechanisms of action, but genistein inhibits NF-κB activity through Notch-1 signaling, causing G2/M arrest, anti-proliferation, and proapoptotic effects in TNBC [137]. Genistein-induced apoptosis and Notch suppression are directly linked to cell cycle inhibition. EMT stands out among the majority of cancer types and is strongly linked to both treatment resistance and tumor development, especially in pancreatic cancers [141].

### Quercetin

Quercetin is derived from the Quercus-named quercetum (oak woodland). It is abundant in various plants, such as apples, berries, brassica vegetables, capers, grapes, onions, tea, and tomatoes, as well as seeds, nuts, flowers, bark, and leaves [142]. Additionally, quercetin has numerous biological benefits, including protection against metabolic disorders, and anti-inflammatory, anti-oncogenic, antioxidant, antibacterial, and immunoprotective properties [143–149]. Microarray profiling has identified MiR-200b-3p as a cell fate factor that is downregulated in pancreatic ductal adenocarcinoma. Targeting the Notch-1 3′UTR disrupts Notch signaling, preventing CSC self-renewal and proliferation, altering symmetrical to asymmetrical cell division mode, and initiating cell differentiation [150]. Quercetin may be able to modify MiR-200b-3p to restore normality [150]. To ensure its successful future, more plausible proof of the benefits of the current treatments should be presented. Flavonoid and hedgehog suppressed Notch, reducing cell death and proliferation markers like caspase-3, cyclin D1, and Ki-67, indicating improved hepatic cellular integrity in vivo [151]. Mice that received quercetin 100 mg/kg dissolved in saline, p.o., once daily also showed a suppression of CK2α activity. However, ectopic NICD has the potential to reverse such successful therapeutic effects and promote enhanced proliferation of cancer cells [152]. Quercetin-3-methyl treatment significantly inhibited BC cell growth and progression by targeting Notch-1, PI3K, and Akt signaling [153]. Furthermore, quercetin-3-methyl ether may be a promising treatment for triple-negative and hormone-sensitive BC due to its ability to inhibit EMT and CSC formation [153].

### Ellagic acid

Ellagic acid (EA) (Fig. 5) is a polyphenol compound extracted from various herbs like paeoniae paeoniae, raspberry, Chebule, walnut kernel, myrrh, loquat leaf, pomegranate bark, quisquite, and fairy herb [154, 155]. EA, gallic acid, and quercetin reduce cancer stem cell survival by downregulating the β-catenin/p-GSK3β signaling pathway [156]. EA influences glioblastoma cell cycle development through the Akt Notch-1 pathway [157]. EA promotes EMT and inhibits Bcl-2, CDK2, and CDK6 expression, causing G0/S arrest in cancer cells and preventing U87 xenograft growth in vivo [157]. The concentration may not be physiologically accessible in plasma due to extensive crosstalk between Notch and PI3K/Akt, indicating that blocking Notch expression can lower PI3K/Akt activity [158, 159]. EA treats human pancreatic ductal adenocarcinoma in Balb/c nude mice by blocking Akt, Shh, and Notch pathways, with gemcitabine and ZSTK474 combination enhancing effects [160]. A study

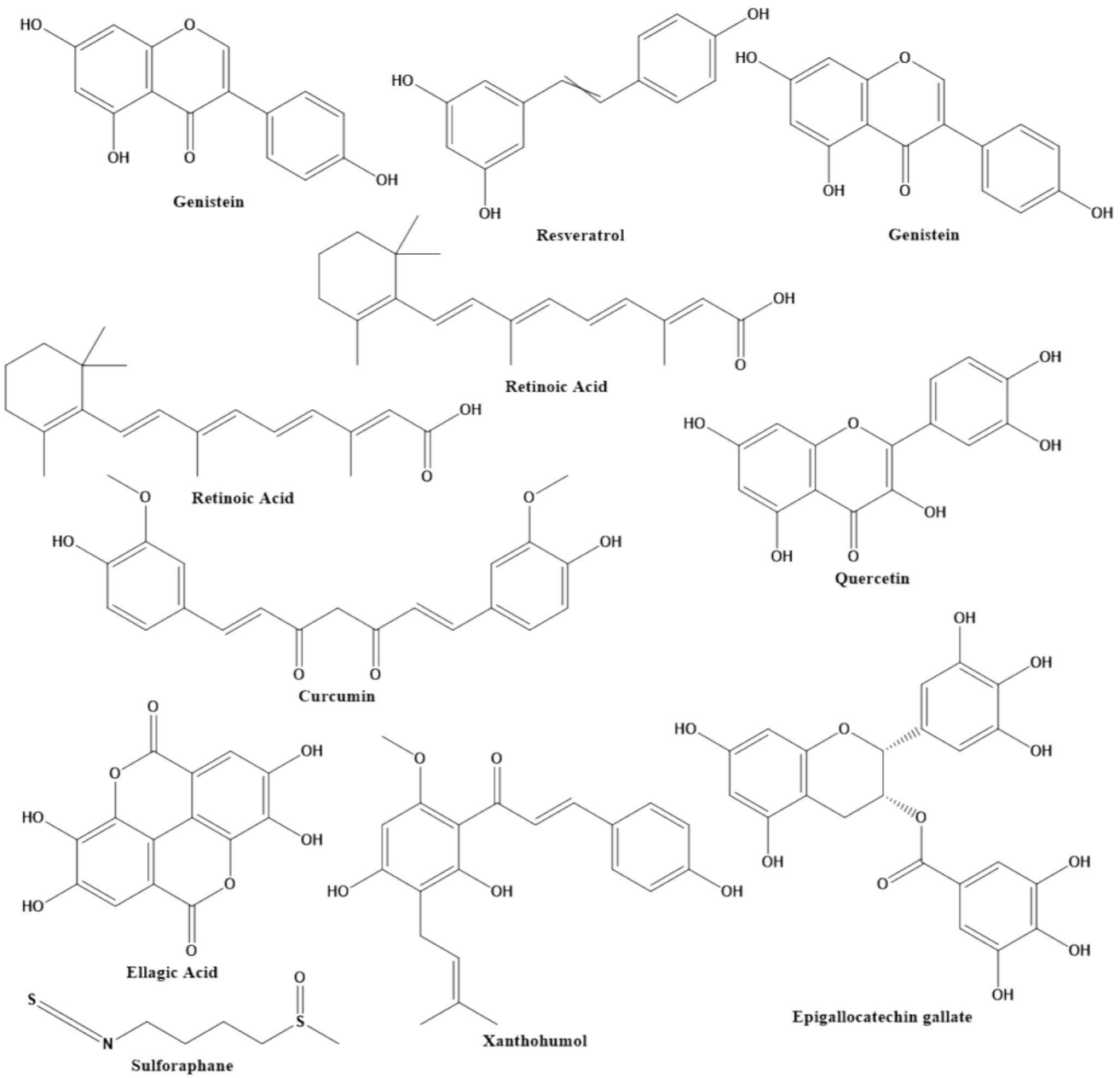



**Fig. 5** Chemical structure of selective bioactive compounds

involved a PANC 1-bearing xenograft that was gavaged daily with EA (0 or 40 mg/kg body weight) for six weeks [160].

### Xanthohumol

Xanthohumol, a prenylated chalcone found in Hop (*Humulus lupulus*) [161]. Xanthohumol (Fig. 5) has numerous anti-inflammatories, anti-microbe, antioxidant, immuno-regulatory, anti-virus, antifungal, anti-genotoxic, antiangiogenic, and antimalarial properties, demonstrating potent cancer-fighting properties [162–164]. In vitro studies revealed that xanthohumol significantly reduces cell viability, causes G0/G1 cell cycle arrest, and apoptosis, while in vivo tests validate its actions by altering apoptotic regulators and controlling cyclins [165]. It acts as a tumor suppressor in xenografts, preventing the growth of tumors [165]. The highly invasive F10 subclone of B16 melanoma cells is particularly affected [166], Isoxanthohumol inhibits Notch-1, β-catenin, and Oct3/4, causing cell pluripotency loss. It increases melanoma cell sensitivity to paclitaxel, creating a barrier against tumor growth and proliferation. This is a significant discovery that opens the door to identifying more potent

combinations of treatments in clinical trials. Unfortunately, there is no comparison of the safety, prognosis, and cost of isoxanthohumol with paclitaxel with other treatments or currently available chemopreventive medications. The study found that xanthohumol dose dependently suppressed Notch family members by reducing mRNA and protein levels, inhibiting NF-kB and PI3K/Akt activity [167].

#### Retinoic acid

Retinoids are synthetic or natural derivatives of vitamin A, commonly known as retinol and retinyl ester, which are dietary forms of vitamin A [168]. Retinoids inhibited Notch expression and signaling in cancer cells, particularly in breast and ovarian cancer [169–171]. ATRA was found to suppress the Notch-3 protein in MDA-MB-231 breast cancer cells [172]. Notch-1 was suppressed in neuroblastoma [173] and pancreatic cancer cell lines [174] by the retinoids 4-HPR, Cl-AHPC, and AHP3. Neuroblastoma cells expressed E-cadherin in response to the retinoid 4-HPR [173]. On the other hand, 13-cis retinoic acid-treated neuroblastoma cells showed more migration in a Notch-independent manner as compared to untreated cells. 13-cis retinoic acid administration raised the proportion of Annexin-V-positive cells and caused cell cycle arrest [175].

#### Sulforaphane

Sulforaphane, often referred to as [1-isothiocyanato-4-(methylsulfinyl)butane], is an aliphatic isothiocyanate. Cruciferous vegetables, including broccoli, cauliflower, cabbage, and Brussels sprouts, are the primary source of their precursor, glucoraphanin [176]. In prostate cancer cells, the isothiocyanate sulforaphane, which comes from cruciferous vegetables, upregulated the expression of NICD-1, -2, and -4 while inhibiting the production of full-length Notch-1, -2, and -4 proteins [177]. Sulforaphane was found to increase Hes1 reporter activity in PC-3 and LNCaP prostate cancer cells [177]. Additionally, sulforaphane effectively blocked Notch-1, preventing gemcitabine from increasing its expression in pancreatic cancer cells in vitro cultured [15]. Moreover, sulforaphane, administered after grafting and pretreated with MiaPaCa2 pancreatic cancer cells before grafting, effectively suppressed tumor development in xenograft nude mice [15], indicating sulforaphane's chemopreventive and anticancer functions in vivo.

#### Vitamin D

The sunshine vitamin is vitamin D. When exposed to sunlight, the skin's 7-dehydrocholesterol absorbs ultraviolet B rays and transforms them into previtamin D3 [178]. There are inconsistent findings on vitamin D's effectiveness as a notch modulator. 1,25-dihydroxyvitamin D3 therapy did not affect Notch-1, Jagged1, Notch-2, Notch-4, and Jagged1 protein expression in keratinocytes or glioblastoma cell models [179, 180]. BXL0124 quickly caused MCF10DCIS.com cells to produce the Hes1 message and protein [181]. Hes1 knockdown with siRNA partly undid the reduction of NICD-1, Jagged2, and c-Myc protein caused by BXL0124 [182]. A study found that tumor tissue from SKOV-3 xenograft nude mice treated with vitamin D analog MT19c showed increased DNA fragmentation and lower expression of Notch system components [183].

#### Silybin

Silybin, derived from Silybum marianum, exhibits numerous beneficial properties, including cytoprotective, anti-inflammatory, antioxidative, anti-fibrotic, and antiviral effects [184]. Silybin is a well-known anti-inflammatory, hepatoprotective, antiviral, neuroprotective, and cardioprotective compound that is mostly utilized in chronic liver disease. It is extracted from milk thistle seeds. It is evident from the results that silybin (Table 1) is an effective notch modulator. Notably, recombinant human Jagged1 reduced the anticancer efficacy of silybin, indicating that Jagged1 might be used as an anti-tumor target [185, 186].

#### Other agents

Honokiol treatment, either alone or combined with a single 5 Gy dose of ionizing radiation, reduced sphere formation and cell survival [31, 195]. The combination of ionizing radiation and honokiol significantly reduced in vivo tumor development [196]. The Indian Winter cherry leaves contain lactone withaferin A, which inhibits NICD-1 and promotes the expression of NICD-2, NICD-4, and RBP-Jκ reporter activity in breast cancer cells [197]. Despite being Notch independent, withaferin A inhibited ALDH1 activity [198]. Citrus fruits contain hesperetin, a flavonoid that stimulates Notch-1 signaling, causes apoptosis, and causes differentiation markers to be expressed in ATC cells [199]. PeiTC, an isothiocyanate from cruciferous vegetables, has been found to inhibit Notch-1 and Notch-2 levels in pancreatic cancer cells, reduce cell proliferation, and induce apoptosis [200]. PEITC effectively targeted differentiated cells and CSCs, reducing NICD-1 expression in HER2-positive breast and ovarian cancer cells [201].

### Bioactive compounds modulate the Notch signaling pathway

#### Gamma-secretase inhibitors

The gamma-secretase complex, consisting of Presenilin, Nicastrin, APH1, and PEN2 proteins, is crucial for the

**Table 1** Bioactive compounds on Notch and other pathways may interact with cancer

| Bioactive compounds | Type of cancer | Cross talk | Finding | References |
|---|---|---|---|---|
| Curcumin | Pancreatic cancer | Notch, Hippo | Overexpression of YAP promotes cell division, while curcumin reduces TAZ and YAP expression, inhibiting Notch-1 expression | [187] |
| Resveratrol | Ovarian cancer | Notch, STAT3, Wnt | Resveratrol and AG490 exhibit varying inhibitory effects on human ovarian cancer cells. AG490 suppresses OVCAR-3 and CAOV-3 cells similarly to resveratrol | [106] |
| Berberine | Gastric cancer | Notch, MAPK, NF-κB | Exhibited anti-GC effects in several pathways, such as Notch, MAPK, and NF-κB signaling pathways | [188] |
| EGCG | Liver cancer | Notch, Hedgehog, NF-κB | Showed the strongest apoptotic potential, while HNK caused necrosis induction and lethal effects on parental cells | [96] |
| Quercetin | Breast cancer | Notch, PI3K/AKT | Inhibited cell growth, induced apoptosis, suppressed invasion and inhibited the EMT process | [153] |
| Artemisinin | Breast cancer | Notch, VEGF, HIF-1 | Suppressed the expression of notch signaling-related components, such as Notch-1, Dll4, and Jagged1 | [189] |
| Withaferin A | Colon cancer | Notch, JNK | Suppressed Notch-1 signaling in colon cancer cell lines, downregulating pro-survival pathways and triggering c-Jun-NH2-kinase-mediated apoptosis | [190] |
| Genistein | Breast cancer | Notch, NF-κB | Decreased the expression of Bcl-2, Bcl-xL, and cyclin B1, possibly due to NF-κB activation through the Notch-1 pathway | [137] |
| Nimbolide | Oral cancer | Notch, VEGF, MMP | Upregulated RECK by targeting miR-21 and HIF-1α in cell lines and a hamster oral carcinogenesis model | [191] |
| Okadaic Acid | Breast cancer | Notch, PI3K/AKT, NF-κB | NF-κB is activated in human breast cancer MDA-MB-231 cells via Notch-1 | [192] |
| Triptolide | Gastric cancer | Notch, NF-κB | Inhibited the growth and spread of gastric tumors in xenograft mice, thereby suppressing the invasion, migration, and carcinogenicity of gastric cancer cells | [193] |
| Trichostatin A | Gastric cancer | Notch, NF-κB | Down-regulated Notch-2 and up-regulated Notch-1 and Hes1, but PD98059 boosted Trichostatin A's capacity to down-regulate the phospho-histone H3 protein | [194] |
| Silybin | Breast cancer | Notch, AKT, ERK | Induced cell death in human breast cancer cells by down-regulating notch-1/ERK/Akt signaling in a ROS-dependent manner | [186] |

production of NICD. Lung, colorectal, melanoma, and ovarian malignancies are among the tumors for which inhibition of secretase activity has demonstrated strong anti-tumor effectiveness [11]. Numerous gamma-secretase inhibitors (GSIs) have demonstrated anticancer efficacy and progressed from preclinical testing to early clinical phases [202]. Cucurbitacin B and I inhibit colon cancer tumor development by binding to Notch-1 and restraining downstream genes, lowering Notch receptor expression, limiting gamma-secretase activity, and reducing NICD generation [202, 203]. Celastrol and triptolide effectively inhibited Notch-1 expression and its downstream target proteins in TNBC, thereby regulating stem cell renewal [204]. Furthermore, quercetin also reduces the expression of the gamma-secretase complex's five proteins (presenilin1, presenilin2, Nicastrin, APH1, PEN2) in colorectal cancer [152]. Quercetin can potentially reduce the toxicity of GSIs and enhance their overall anti-tumor activity when combined with ionizing radiation [205] or a gamma-secretase inhibitor [206].

### Notch transcription complex inhibitors

The Notch signaling pathway's interaction between NICD and CSL determines gene activation or deactivation. Phytochemicals can inhibit cancer by increasing co-repressor expression and decreasing CSL and NICD binding. Silybin can inhibit NICD activity in human cancer cells by activating the apoptotic pathway, which in turn reduces the Notch signaling system. Silybin decreases Notch-1 expression and RBPJ activity in hepatocellular cancer, a process that relies on CSL [185], suggesting that a clever tumor therapeutic approach is to block the interactions between CSL and N1ICD. Resveratrol regulates DNA methylation patterns in human breast cancer cells, inhibiting cancer-causing Notch signaling, by controlling MAML2 transcriptional activity through epigenetic processes [111].

### Notch downstream target genes inhibitors

The transcription of downstream target genes, particularly the Hes and Hey protein families, is the final step in Notch signaling [207]. Hes1 is found to activate the Notch signaling system, which in turn promotes proliferation and inhibits apoptosis. It has been demonstrated that natural products such as oleandrin and Cowan suppress Hes1/5 expression, hence regulating the course of T-ALL [208, 209].

## Crosstalk between Notch and other oncogenic pathways

Notch signaling is a crucial gene that acts as both a tumor promoter and a tumor suppressor in various human malignancies. Numerous proteins are upregulated when the Notch signaling system is activated, and these factors then send bidirectional signals between endothelial, stromal, and malignant cells [32, 210]. Notch signaling is expected to interact with growth factors, oncogenic pathways, and transcription factors like EGFR, TGF-β, VEGF, Wnt, Hedgehog signaling, and PI3K/AKT [207].

### Interacting with developmental signaling pathways

The Wnt and Hedgehog signaling pathways coordinate across various forms of cancer and are among the developmental routes with which the Notch pathway interacts throughout embryogenesis [207]. A recent study found that Notch–Wnt communication plays a role in breast carcinogenesis, as Notch ligand production prevented Wnt1-induced transformation of human mammary epithelial cells [211]. ESC-3, a new cytotoxic drug, inhibits tumor development in an ovarian cancer xenograft model by blocking the Notch and Wnt/β-catenin pathways, leading to apoptosis [212]. Emodin is known to inhibit the Wnt pathway in human glioma stem cells by decreasing the amount of active β-catenin [213]. A study found that β-catenin, when upregulated by the expression of the Notch ligand Jagged1, can activate Notch signaling [34, 214]. Bruceine D inhibits Jagged1 in a reversed manner after overexpression and synergistically after β-catenin knockdown [215]. Nevertheless, in Jagged1 knockdown cells, β-catenin levels did not alter [215]. Notch inhibitors like emodin and resveratrol may prevent β-catenin-induced cancer, while the active Wnt signal enhances β-catenin accumulation in the nucleus, leading to cancer development [216]. Resveratrol inhibited ovarian cancer cell growth by reducing β-catenin and Hes1 expression, indicating simultaneous suppression of Notch and Wnt signaling's biological roles [106]. A developmental signaling system known as the Hedgehog is crucial for carcinogenesis, tissue polarity, tissue regeneration, and embryogenesis [217, 218]. The Hedgehog pathway involves receptors, intermediates, and inhibitors, influenced by transcriptional factors like Ci/Gli and is influenced by SUFU and COS2 [219]. The brain development in sonic hedgehogs, the skeleton in Indian hedgehogs, and the gonadal system in desert hedgehogs are influenced by their environment [220]. The Notch signaling system regulates Hedgehog, primarily through its downstream effector, which controls Gli levels and the transport of Hedgehog components [221]. As a result, Notch target genes are essential for regulating the transcription of Gli genes [222]. *P. granulata*-derived physciosporin reduced Gli, Hes1, and CSL transcriptional activity [223]. Furthermore, by binding directly to NICD, NUMB endocytic adaptor protein (NUMB) inhibits NICD from starting gene transcription, hence adversely regulating Notch signaling [224]. Through the action of Itch, NUMB selectively targets Gli1 for ubiquitination and suppresses Hedgehog signaling [225]. Quercetin inhibits Hedgehog and NUMB signaling pathways, reducing tumor development, suggesting NUMB as a potential cancer biomarker [151]. Furthermore, the Hedgehog signaling pathway modulates the Notch pathway, primarily by inhibiting Hedgehog downstream effectors, including Hes1 and Gli proteins [226, 227]. Hes1 expression in human Hep2 cells can be regulated by hedgehog signaling, but EGCG, an inhibitor of NICD, can counteract this effect [96]. Consequently, Hes1 synthesis may be promoted by the Hedgehog signaling pathway's influence on NICD activity [228]. Cordycepin inhibited Gli transcription in human TNBC cells, reducing the expression of Notch-1, Notch-3, Jagged1, and Hes1 [229]. Gli's knockdown inhibited cordycepin's effects on apoptotic, EMT, and Notch pathways, highlighting its significance in cordycepin regulation of Notch in breast cancer [229]. There is evidence that Hedgehog signaling during carcinogenesis induces the Notch ligand, Jagged2 [230]. Cyclopamine inhibits the expression of Notch-1, Notch-2, Notch-3, Jagged2, and DLL1 in sonic hedgehog odontogenic keratocytes, leading to their downregulation [231].

### Interacting with growth factors

Growth factors like EGFR, TGF-β, PDGF, and ErbB2 can impact cancers through oncogene gene mutations, are examples. Growth factor pathways, such as invasion, proliferation, and tumor growth, are linked to the development of malignancies [232]. It has been found that the Notch-EGFR crosstalk plays a part in breast [233], lung [48], and brain [234] cancers. The human ErbB2-negative tumor cell lines experienced a significant suppression of growth, leading to programmed cell death due to a decrease in Notch-3 activity [235]. However, the Notch pathway may also be regulated by EGFR signaling. Emodin inhibited human glioma stem cell proliferation by breaking down EGFR/EGFRvIII, thereby preventing the activation of stemness signaling pathways,

including the Notch pathway [213]. The non-epithelial tumor stroma is the main target of PDGF, which is generated in carcinomas and promotes angiogenesis [236, 237]. The PDGF receptor is currently identified as a novel Notch target gene in the available literature [238, 239]. The activation of Notch-1 is directly linked to the aggressiveness of breast cancers, and PDGF-D plays a crucial role in this [240]. Downregulating PDGF-D can potentially reverse the EMT and delay the onset of colorectal cancer by inactivating the Notch-1/Twist1 axis [241]. Lycopene inhibits the development of certain cancer cells, although no published results have been found on natural substances altering PDGF-D and Notch signaling interactions [242]. Lycopene's direct binding to PDGF-BB suggests its potential anti-tumor properties, as it has been shown to suppress PDGF [242]. TGF-β, a multifunctional cytokine, plays a crucial role in cancer pathophysiology by influencing adhesion, apoptosis, differentiation, and cell proliferation [243]. TGF-β's role in cancer is influenced by signaling pathways like Hedgehog, Wnt, PI3K/AKT, Notch, and RAS-ERK. Heyl, a downstream effector, inhibits TGF-β activity [244]. Furthermore, garlic-derived Z-ajoene has shown a range of biological actions, including anti-tumor, antioxidant, and anti-proliferative properties [245, 246]. Z-ajoene's action on glioblastoma multiforme cancer stem cells is primarily mediated by TGF-β, which also reduces levels of Notch target genes [246]. Moreover, the preservation of stem cell characteristics in cancer cells depends on the TGF-β pathway [247]. VEGF, a vital angiogenic factor in blood vessel formation, is frequently overexpressed in human malignancies, resulting in reduced patient survival rates and cancer spread across multiple tumors [248, 249]. Limiting VEGF may increase tumor susceptibility to anti-Notch treatment, as survivin shRNA and EGCG significantly reduced angiogenic factors before inhibiting Notch-1 expression in neuroblastoma [92]. Nimbolide, extracted from neem leaves and blossoms, inhibited Notch and VEGF signaling pathways and reduced MMP activity by targeting miR-21 [191]. By suppressing the expression of Notch, HIF-1, VEGF, and NF-κB, curcumin may also reduce the size and weight of tumors [250]. Notch signaling controls VEGF ligand and receptor production, as seen in histiocytic lymphoma, where quercetin inhibited VEGF and HIF-1α production after decreasing Notch-1 expression [251]. Artemisinin reduces breast cancer levels by downregulating Notch-1, DLL4, and Jagged1 expression [189].

### Interacting with oncogenic kinases and transcription factors

Genistein's ability to deactivate NF-κB DNA-binding activity was partially inhibited in BxPC-3 cells transfected with cDNA by the overexpression of Notch-1 [252]. By blocking NF-κB activity through the Notch-1 pathway, genistein also prevents the formation of tumors in triple-negative breast malignancies [137], colon cancers [138], and pancreatic cancers [252]. Curcumin inhibits NF-κB DNA-binding activity, suppresses Notch-1 expression, and prevents Notch-1 activation [121]. Notch family members' transcription is controlled by NF-κB subunits. This conclusion is corroborated by [253], research demonstrated that the p50 subunit could not connect to DNA in NTera-2 cells and was only bound by the N-terminal portion of Notch-1 NICD. Trichomotatin A, produced from Streptomyces, regulates NF-κB and p21WAF1/CIP1 in gastric cancer cells, enabling apoptosis and growth arrest without involving the Notch system [194]. Berberine is a drug that regulates the expression of circRNA, a key component in the regulation of the Notch, MAPK, and NF-κB signaling pathways [188]. Bethanidin, which has the potential to cure CLL cells by directly binding to SENP2, but no natural compounds currently control SENP2 activity in hematologic malignancy treatment [254]. The Notch and NF-κB pathways regulate each other's activity to promote the growth of cancer. Inflammatory illness is often regulated by the Notch-NF-κB network [255]. Inflammation influences tumor formation and treatment response, potentially promoting or inhibiting growth, and potentially impacting therapy efficacy [256]. Small-molecule inhibitors targeting NF-κB, downstream of Notch, may disrupt interaction and lower inflammation, potentially replacing Notch blockers. Increased signaling in the PI3K/AKT pathway leads to various transformational processes in malignancies [257, 258]. Additionally, mTOR may phosphorylate AKT [259]. A key factor in encouraging EMT along the course of cancer development is the PI3K/AKT pathway [260]. Prostate cancer [261], T-ALL [17], colon cancer [262], brain cancer [193], and breast cancer [153] have all been linked to crosstalk between the PI3K/AKT and Notch pathways. Research indicates that Withaferin A inhibits Notch-1 activation, leading to a decrease in the expression of Bcl-2 and pAKT [262, 263]. ROS-dependent downregulation of Notch-1 causes cell death by controlling AKT signaling and PTEN expression. Curcumin, a Notch inhibitor, raises PTEN expression and lowers AKT phosphorylation in chronic myelogenous leukemia [264]. Notch prevents PI3K/AKT dephosphorylation by blocking PTEN and PP2A activation, thereby promoting cancer progression [192]. Furthermore, resveratrol kills ovarian cancer cells by downregulating Notch-1/PTEN/AKT signaling [263]. AKT regulates the Notch signaling pathway, which is linked to genistein's ability to induce cell growth inhibition and death in prostate cancer [261]. Conversely, in T-ALL cells, resveratrol inhibits Notch signaling, which lowers AKT activity and modifies how associated signaling systems function [17].

## Conclusion and future perspectives

In conclusion, the significant impact of naturally occurring bioactive substances on the Notch signaling system suggests potential new cancer treatment avenues. Natural substances have been found to alter the activity of the Notch signaling pathway, depending on the type of cancer cell. Improving normal Notch function promotes differentiation and death in malignant cells, while inhibiting aberrant Notch activation reduces tumor development in various cancer types. Its insights into the specific interactions that bioactive substances have with downstream effectors, ligands, and Notch receptors. Flavonoids like quercetin and curcumin inhibit Notch receptor activation, preventing cell survival and proliferation. They can alter ligand–receptor binding, preventing tumor formation. Combining these substances with other cancer treatments improves effectiveness and reduces side effects, while polyphenols like Resveratrol and EGCG promote normal differentiation. Natural substances demonstrated promising preclinical outcomes in various cancer models, including colon, lung, prostate, and breast cancer. Certain substances are undergoing clinical trials, and preliminary research suggests they may be safe and effective when used alongside traditional treatments. The review discusses challenges in the study, including limited bioavailability, fluctuating patient reactions, and the need for more comprehensive clinical trials despite promising results. Future research should focus on improving the pharmacokinetics of natural chemicals, examining their processes, and conducting extensive clinical trials to assess their long-term safety and efficacy in cancer treatment. These substances provide a potential solution to overcome resistance mechanisms and enhance the efficacy of existing cancer treatments. However, further research is needed to improve pharmacokinetics, bioavailability, and toxicity reduction. Combination medicines, personalized cancer therapy, and extending the use to less well-known cancers are also crucial. Clinical trials, standardization, and long-term trials are also needed to confirm the safety and therapeutic effectiveness of these substances. Despite promising results, there are significant research gaps in the clinical translation of natural chemicals due to their low bioavailability, inconsistent patient responses, and inadequate mechanistic understanding. The review highlights the limited availability of standardized formulations for bioactive compounds, highlighting the need for improved pharmacokinetic characteristics. It suggests exploring advanced delivery methods, high-throughput screening, molecular docking, and clinical trials to determine long-term safety and efficacy. The review suggests incorporating bioactive compounds into personalized medicine strategies for specific cancer profiles, but further research is needed to address bioavailability, distribution, and clinical effectiveness.

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