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Review

Salvia rosmarinus (Rosemary) Extracts Promote Damage to Cancer Cells In Vitro Partly Through Antioxidant Effects—A Narrative Review

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Abstract

Plant-based compounds with antioxidant, anti-inflammatory, and modulatory effects have shown important protective roles against cancer. *Salvia rosmarinus* Spenn. (formerly *Rosmarinus officinalis* L.) belongs to the Lamiaceae family and is commonly known as rosemary. As a medicinal plant, rosemary is notable for its phenolic compounds and bioactive diterpenes, including carnosic acid, carnosol, and rosmarinic acid, which have demonstrated antioxidant and anticancer effects. The scientific evidence on *Salvia rosmarinus* was reviewed to analyze its antioxidant and anticancer activities, examining extract characteristics, methods, models, and mechanisms. A PubMed search was conducted using the terms such as "Rosemary extract," "antioxidant," and "anticancer", including in vitro and in vivo studies. Results showed that *Salvia rosmarinus* extracts, containing large amounts of carnosic acid and carnosol, reduced proliferation, induced apoptosis, caused cell-cycle arrest, and decreased tumor growth in models of colon, breast, prostate, liver, and lung cancers and in leukemia cells, and modulate signaling pathways such as NF-κB, PI3K/Akt/mTOR, Nrf2, and STAT3, helping to protect normal cells and to eliminate tumor cells. Overall, evidence supports *Salvia rosmarinus* potential as an antioxidant and anticancer source. Nevertheless, variability in the physicochemical properties and phytochemical composition of *Salvia rosmarinus* extracts, together with limited safety and pharmacokinetic data, highlights the need for further research and controlled clinical trials to validate their antioxidant and anticancer efficacy.

Keywords: *Salvia rosmarinus* (rosemary); antioxidant activity; anticancer activity; chemoprevention

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1. Introduction

The persistently low success rates of conventional cancer therapies underscore the need to identify more effective therapeutic alternatives. Relevant information on rosemary

extracts and their bioactive compounds regarding their properties as antioxidant and anti-tumor agents was reviewed. In contrast to the previous literature, the interplay between their biochemical and molecular mechanisms is presented in order to show an innovative perspective that not only identifies novel pharmacological candidates, but also elucidates key metabolic pathways to guide the discovery of future therapeutic targets.

1.1. Cancer as a Global Health Challenge

Cancer represents a significant global public health challenge due to its high incidence and mortality rates, as well as its emotional and economic impacts on patients and their families [1]. Currently, cancer represents one of the most significant challenges facing health insurance systems, given the high cost of treatment and the loss or reduction in workforce capacity caused by the disease. The incidence and prevalence of cancer are not expected to decline in the coming years, and annual diagnoses could reach 34.5 million by 2050 [2].

The pathogenesis of cancer encompasses numerous factors, including genetic predisposition, environmental exposure to carcinogens, and unhealthy habits. Collectively, these factors can promote the transformation of normal cells into malignant ones. During this process, cells acquire the ability to proliferate indefinitely while evading the cellular mechanisms that ordinarily suppress growth. Transformed cells also resist the induction of programmed cell death to reach a sufficient number and establish a self-sustaining ecosystem by developing new blood vessels (angiogenesis), which enables them to invade other tissues (metastasis). These characteristics facilitate tumor establishment and progression. Tumor development is further influenced by interactions with the surrounding microenvironment, including immune cells, fibroblasts, endothelial cells, and extracellular matrix components. Together, these elements sustain inflammation, enhance cell survival, and drive disease progression. Cancer is recognized as a heterogeneous group of diseases with complex molecular mechanisms rather than as a single clinical entity. Accordingly, current research emphasizes identifying the specific molecular alterations and signaling pathways involved in carcinogenesis, with the aim of informing prevention strategies, early diagnosis, and targeted therapies. It is a conceptual framework, which accounts for cancer's biological diversity, promotes the development of more precise therapeutic interventions to improve patient survival and quality of life [3–5].

1.2. Oxidative Stress and Its Contribution to Carcinogenesis

Oxidative stress plays a central role in carcinogenesis. The excessive production of reactive species, including the superoxide radical (O_2^-), the hydroxyl radical (HO•), and non-radical species such as hydrogen peroxide (H_2O_2), results from the diversion of electrons that would normally participate in various metabolic processes. These include oxidative phosphorylation via the mitochondrial respiratory chain and redox reactions in the endoplasmic reticulum (ER) and peroxisomes [6]. Oxidative stress also arises from an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the capacity of cellular antioxidants to neutralize them. Under physiological conditions, ROS and RNS regulate cell signaling, proliferation, differentiation, and immune responses. When ROS or RNS production exceeds antioxidant defenses, critical biomolecules, including lipids, proteins, and DNA, undergo oxidation. Oxidative DNA damage can result in base modifications, strand breaks, and chromosomal alterations, increasing the likelihood of mutations in proto-oncogenes, tumor suppressor genes, and DNA repair genes. In addition to their mutagenic effects, ROS function as second messengers that modulate signaling pathways involved in cell survival, proliferation, and inflammation, including NF-κB, AP-1, and Nrf2. These processes alter gene expression and promote abnormal cellular mechanisms that may lead to tumor development. Chronic oxidative stress also

contributes to genomic instability, resistance to apoptosis, angiogenesis, and tumor progression. The effects of ROS depend on their concentration and cellular context: moderate levels are essential for normal cellular function, whereas elevated levels induce oxidative damage and facilitate malignant transformation. Collectively, these observations underscore the importance of redox homeostasis in cancer prevention and progression [3,7–10].

1.3. The Role of Herbal Products and Phytochemicals in Oncology

Herbal products and phytochemicals serve a dual role in oncology to provide the basis for standard chemotherapy drugs and function as complementary agents to manage treatment-related side effects. More than 50% of conventional anticancer drugs are derived directly from natural plant sources. In clinical practice, researchers classify these plant-derived agents into two distinct groups: FDA-approved chemotherapeutic agents and phytochemicals under investigation or used for supportive care in oncology [11]. Herbal medicine has been extensively studied as a potential source of anticancer drugs, given the large number of secondary metabolites with significant pharmacological and biological activities, including antitumor effects [12,13]. Evidence indicates that these phytochemicals modulate signaling pathways implicated in cancer progression, including NF-κB, PI3K/Akt/mTOR, MAPK, and STAT3. Through these mechanisms influence cellular proliferation, apoptosis, angiogenesis, invasion, and metastasis. Certain plant-derived compounds also help maintain cellular redox homeostasis, thereby mitigating oxidative damage associated with carcinogenesis. The therapeutic value of natural products is exemplified by the development of plant-derived agents, such as vinca alkaloids and taxanes, which underscore the potential of botanical sources for novel anticancer therapies. However, the clinical application of many phytochemicals remains limited by challenges such as poor bioavailability, variability in extract composition, and insufficient evidence from rigorously controlled clinical trials. Addressing these limitations requires standardizing herbal extracts and identifying active constituents to ensure reproducibility and facilitate their integration as complementary strategies in cancer prevention and therapy [14–16].

1.4. The Pharmacological Significance of Salvia rosmarinus

Salvia rosmarinus possesses considerable pharmacological value owing to phenolic diterpenes and acids, including carnosic acid, carnosol, and rosmarinic acid, which confer antioxidant, anti-inflammatory, cytoprotective, and antitumor properties [17–20]. In vitro studies using various extracts have demonstrated the inhibition of tumor cell proliferation and the induction of apoptosis through mechanisms involving pathways such as NF-κB, PI3K/Akt/mTOR, and STAT3, alongside the activation of Nrf2, Sestrin-2, and MRP2. These findings link antioxidant activity with antitumor effects [19–23]. In animal models, extracts and compounds derived from them have been shown to reduce tumor size, number, weight, and associated tissue markers in the colon, prostate, breast, skin, and melanoma, while also enhancing the efficacy of chemotherapeutic agents when used as adjunctive therapy [17,20–22].

These reasons have increased interest in bioactive compounds from natural sources, prompting research on plant species that may prevent or complement the treatment of chronic diseases, especially cancer. *Salvia rosmarinus* stands out for its high levels of phenolic compounds and bioactive diterpenes, including carnosic acid, carnosol, and rosmarinic acid, which exhibit antioxidant, anti-inflammatory, and antitumor effects in experimental studies. Evidence suggests that *Salvia rosmarinus* extracts influence multiple pathways in carcinogenesis, including oxidative stress, apoptosis, cell proliferation, angiogenesis, and signaling. Results vary because of differences in extraction, composition, doses, and models, making a full pharmacological assessment difficult. Despite promising studies on their

anticancer effects, findings remain scattered, and challenges such as standardization and limited clinical research persist. A comprehensive review is needed to identify trends, strengths, limitations, and future research directions. Therefore, the scientific evidence on the antioxidant and anticancer properties of *Salvia rosmarinus* extracts was integrated, including their characteristics, preparation, experimental models, mechanisms, and results from in vitro and in vivo studies.

1.5. Botanical and Phytochemical Characterization of Salvia rosmarinus

1.5.1. Taxonomy and Geographical Distribution

Salvia rosmarinus Spenn. (formerly *Rosmarinus officinalis* L.) belongs to the family Lamiaceae, which comprises aromatic and medicinal plants used in cuisine and traditional remedies. It is a perennial shrub, native to the Mediterranean region, that thrives in dry and sunny conditions. Medicinal, aromatic, and culinary applications have led to its cultivation worldwide. Environmental factors, including climate, altitude, soil, and water availability, influence secondary metabolite profiles, resulting in chemical variation and affecting biological properties [24–26].

1.5.2. Main Secondary Bioactive Metabolites

The effects of *Salvia rosmarinus* are primarily attributed to terpenes, flavonoids, and phenolic compounds. Key metabolites, including carnosic acid and carnosol, which are present in extracts, serve as major antioxidants and anticancer agents [26–28]. Rosmarinic and caffeic acids also contribute to the neutralization of ROS and the modulation of cancer-related inflammation [26,29].

Among the identified triterpenes, ursolic acid and oleanolic acid are notable for their antiproliferative and pro-apoptotic effects across various cell models [24]. Ursolic acid reduces ROS in V79 cells, as measured by TEAC and MTT assays [30] and induces apoptosis and inhibits cell migration in human metastatic melanoma (SK-MEL-24) [31]. Oleanolic acid reduces oxidative level in human breast epithelial cells (MCF-10A) [32] and neutralizes the free radicals in mice exhibiting lipopolysaccharide-induced hyperalgesia [33], whereas a reduction in the viability and proliferation in gastric cancer cell lines MKN-45 and SGC 7901 have been reported [34]. It inhibits tumor growth by inducing apoptosis and reducing cell proliferation in mouse xenograft models of colorectal cancer and in the HT-29 cell line [35] and reduces viability and proliferation in melanoma in the A375SM and A375P cell lines [36]. The hexane extract of rosemary contains high concentrations of monoterpenes and other volatile compounds, including α-pinene, β-pinene, borneol, camphene, eucalyptol, limonene, and verbenone, which contribute to the antioxidant, antimicrobial, and anti-inflammatory activities of the species [23,24]. Limonene produces antioxidant and anticancer activities by counteracting the increase in ROS production caused by Aβ1-42 oligomers in primary cortical neurons [37] and in the percentage of apoptotic cells throughout cell-cycle arrest, and inhibition of migration in the T24 bladder cancer cell line [38], respectively. Recently, four previously undescribed diterpenes were characterized: 18-hydroxycarnosol, 18-acetoxyrosmanol, 18-acetoxycarnosol, and 18-acetoxy-7-O-methylrosmanol. Of these, 18-hydroxycarnosol demonstrated antiproliferative activity against the K562 leukemia cell line, attributed to its antioxidant activity and inhibition of lipid peroxidation [28,39].

The ethanolic extracts also contain diverse flavonoids, including apigenin, hesperidin, kaempferol, luteolin, and quercetin, which are well known for their antioxidant and chemopreventive properties [25,26]. Apigenin raises glutathione levels and lowers MDA and catalase activities in a mouse depression model [40] and shows high capacity for absorbing oxygen radicals from UVA and UVB radiation in human keratinocytes [41], as well as intrin-

sic and extrinsic pathways of apoptosis in colon carcinogenesis cells [42–44]. Kaempferol increases apoptosis and decreases cell proliferation in HL-60 cells [45]; inhibits the migration and accumulation of renal cancer cells in the 786-O (CRC) cell line [46]; induces apoptosis and suppresses growth in HeLa cervical cancer cells [47]; induces cell-cycle arrest and promotes apoptosis in the gastric cancer cell lines MKN28 and SGC7901 [48]. In addition, a selective cytotoxicity in hepatocytes of the hepatocellular carcinoma cell has also observed in rats [49]. As antioxidant, luteolin mitigates the increase in lactate dehydrogenase (LDH), malondialdehyde (MDA) and ROS in cells exposed to ammonia [50]. Selective cytotoxicity in hepatocytes of the hepatocellular carcinoma cell was noticed in rats [49]; it exhibits radiosensitizing activity and induces cell death in lung cancer in the NCI-H460 and NCI-H1299 cell lines [51]; induces apoptosis and caspase-3 activation and inhibits the cell cycle at the G2/M phase in human esophageal carcinoma cells [52]; promotes apoptosis and inhibited cell migration in lung cancer in the NCI-H460 cell line [53] and decreases cell viability in the HT-29 human colon cancer cell line [54]. Finally, quercetin induces the expression of antioxidant enzymes in the liver in adipose tissues of mice with a quercetin-rich diet [55]; has a neuroprotective influence on manganese-induced neurotoxicity by improving neurobehavioral performance and its ability to maintain AChE and antioxidant enzyme activities with the concomitant suppression of oxidative insult [56]. As an anticancer, it reduces viability, induces apoptosis, and inhibits the cell cycle in the G2/M phase in triple-negative breast cancer cells [57]; produces BCL2/BAX-mediated apoptosis, necrosis, and mitotic catastrophe; and inhibits the migratory potential of A549 cells in lung cancer [58], but also reduces tumor size and the cumulative number of papillomas in mouse skin cancer [59].

1.5.3. Variability in Phytochemicals Based on Geographical Origin and Extraction Techniques

The chemical composition of *Salvia rosmarinus* varies depending on environmental conditions and extraction methods. Organic solvent extracts differ from water-based extracts; hexane extracts are richer in lipophilic compounds, such as α-pinene, β-pinene, carnosic acid, carnosol, ursolic acid, and oleanolic acid [24]. Ethanolic extracts contain higher concentrations of phenolics and flavonoids, including rosmarinic acid, caffeic acid, luteolin, quercetin, kaempferol, and hesperidin. Aqueous extracts primarily contain carnosol, rosmarinic acid, caffeic acid, ursolic acid, hesperidin, and luteolin, compounds that are preferentially extracted by polar solvents [26]. It is known that geographic, seasonal, and solvent variations significantly affect the phytochemical profile of *Salvia rosmarinus*; Mediterranean samples extracted with alcohol in March had the highest polyphenol content. LC/MS analysis identified 28 novel compounds and high levels of monoterpenes, including 1,8-cineole and camphor. These findings underscore the importance of environmental and extraction factors in determining the plant's therapeutic potential [60].

These phytochemical variations partly account for differences in the antioxidant and anticancer activities of *Salvia rosmarinus* extracts. Accordingly, chemical characterization and standardization are essential for comparing results and supporting the development of future therapies [24,28].

1.5.4. Antioxidant and Cytotoxic Activities of *Salvia rosmarinus* Extracts or Metabolites Depend on the Nature of the Extraction

Experimental evidence indicates that *Salvia rosmarinus* extracts exhibit biological activity influenced by their phytochemical composition depending on the extraction methods. Studies have reported effects on cell proliferation, apoptosis, oxidative stress, inflammation, and tumor growth across various models. Table 1 summarizes the methods employed and the key findings.

Table 1. Studies assessing the antioxidant and anticancer properties of extracts and main bioactive metabolites derived from *Salvia rosmarinus* extracts.

Study Design	Type of Extract/Compound	Extraction Method & Plant Part	Experimental Model & Treatment Conditions	Performed Assays	Quantitative & Main Results
Primary Study (Original)	Hexane extract [24]	Hexane extraction & nano-encapsulation; leaves	In vitro phytochemical & photoageing assays; (30–300 mg/mL)	Phytochemical profiling, antioxidant capacity, oxidative stress biomarkers	Identified α-pinene, β-pinene, borneol, camphene, carnosic acid, carnosol, ursolic acid, and oleanolic acid; IC_{50} of 221.6 ± 11.8 µg/mL, to scavenge DPPH radicals.
Secondary Literature (Review)	Ethanol, aqueous, and hexane extracts [25]	Solvent extraction by polarity; leaves	Human cancer cell lines (in vitro)	Phytochemical quantification & antiproliferative assays	Ethanolic extracts yielded higher total phenolics and flavonoids; dose-dependent tumor cell growth inhibition.
Primary Study (Original)	Essential oil (ROLEO) vs. methanolic extract (ROLME) [27]	Distillation/methanol extraction; leaves	In vitro antioxidant, anticancer, enzyme inhibition & in silico molecular docking (low-dose evaluations); specific IC_{50} in MCF-7 and Hep-G2 cells	GC-MS profiling, TPC, TFC, α-amylase/α-glucosidase inhibition, anticancer & antibacterial assays, docking	Identified 73 compounds in ROLEO vs. 20 in ROLME. ROLEO had higher TPC (49.34 ± 2.84 mg GAE/g) and TFC (24 ± 1.47 mg QE/g) than ROLME (38.13 mg GAE/g; 19 mg QE/g). Thymol showed strong binding to caspase-3; ROLEO exhibited superior low-dose anticancer and antioxidant activity.
Primary Study (Isolated Metabolite Reference)	Pure quercetin (flavonoid constituent present in *Salvia rosmarinus*)	Commercial/isolated compound (comparative reference; not extracted directly in study)	In vivo DMBA/croton oil-induced skin carcinogenesis in Swiss albino mice; oral administration of 200 and 400 mg/kg/day for 16 weeks	Histopathology, tumor incidence/size, serum liver enzymes (GOT, GPT, ALP, bilirubin), antioxidant enzymes (GSH, SOD, CAT), lipid peroxidation, DNA damage	Reduced tumor size and cumulative papilloma count; extended tumor latency period. Increased endogenous antioxidants (GSH, SOD, CAT) inhibited lipid peroxidation, lowered serum toxicity markers, and significantly reduced DNA damage.
Primary Study (Original)	Ethanolic, petroleum ether, chloroform, and methanolic crude extracts [26]	Solvent extraction (four polarities); fresh aerial parts (stems and leaves, Albaha region, Saudi Arabia)	In vitro human cancer cell lines (MCF-7 breast and HCT-116 colon) and microbial strains (*B. subtilis*, *S. aureus*, *E. coli*, *C. albicans*); concentrations tested to determine IC_{50}	GC-MS phytochemical profiling, MTT cytotoxicity assay, antimicrobial susceptibility assays	Petroleum ether extract contained 46.5% methyl-cyclohexane and showed potent cytotoxicity against MCF-7 (IC_{50} = 3.77 µg/mL) and HCT-116 (IC_{50} = 3.09 µg/mL). Chloroform extract inhibited MCF-7 (IC_{50} = 12.7 µg/mL). Petroleum ether and chloroform extracts also showed broad antibacterial and antifungal activity.

Table 1. *Cont.*

Study Design	Type of Extract/Compound	Extraction Method & Plant Part	Experimental Model & Treatment Conditions	Performed Assays	Quantitative & Main Results
Secondary Literature (Narrative Review)	Whole-rosemary extract and isolated polyphenols (primarily carnosic acid and rosmarinic acid) [21]	Diverse extraction methods (aggregated from the reviewed literature; predominantly leaves)	Synthesized in vitro cancer cell lines and in vivo animal models (doses and durations vary across primary studies)	Review of cell proliferation, apoptosis, survival signaling molecules, and antioxidant/anti-inflammatory markers	Summarizes preclinical evidence showing that rosemary extract, carnosic acid, and rosmarinic acid inhibit uncontrolled proliferation, overcome apoptosis resistance, and modulate key oncogenic signaling pathways.
Secondary Literature (Narrative review)	Whole-rosemary extract (including FDA/EFSA-approved food-grade compositions) vs. isolated constituents (carnosic acid, carnosol, ursolic acid, rosmarinic acid) [19]	Diverse extraction methods (aggregated from the literature; predominantly leaves)	Synthesized in vitro cancer models and in vivo animal studies (heterogeneous doses and durations across reviewed studies)	Synthesis of antitumor molecular mechanisms, antioxidant-independent pathways, safety profiles, and chemotherapeutic interactions	Evaluates the use of whole-rosemary extracts as safe complementary agents in oncology compared to isolated compounds; highlights non-antioxidant molecular mechanisms and summarizes interactions with conventional anticancer drugs.

2. Results

2.1. The Antioxidant Activity of Salvia rosmarinus Extracts

2.1.1. Biological Basis of Oxidative Stress

Oxidative stress arises when the production of ROS exceeds the cell's antioxidant capacity, resulting in the oxidation of lipids, proteins, and nucleic acids and contributing to chronic diseases, including cancer. Extracts of *Salvia rosmarinus* contain bioactive metabolites, such as carnosic acid, carnosol, and rosmarinic acid, which are recognized for their antioxidant properties. These compounds help reduce oxidative damage and maintain redox balance [17,21].

2.1.2. Free Radical Scavenging and Lipid Peroxidation

The phenolic compounds in *Salvia rosmarinus*, including carnosic acid and carnosol, act as electron and hydrogen donors, neutralize free radicals, and reduce cellular oxidative damage because of their strong reducing capacity and ability to stabilize reactive oxygen species [17]. Extracts of *Salvia rosmarinus* inhibit lipid peroxidation, a key antioxidant process. In human oral squamous cell carcinoma (OSCC) cells, *Salvia rosmarinus* extract decreased malondialdehyde (MDA) levels, a marker of oxidative damage, indicating a reduction in intracellular oxidative stress [61].

2.1.3. Activation of Nrf2 and Regulation of Antioxidant Enzymes

Activation of Nrf2 by *Salvia rosmarinus* extracts upregulates antioxidant genes and enhances cellular protection against oxidative stress, thereby preventing ROS-mediated damage. These findings highlight carnosic acid and phenolics as key activators [17]. In addition to activating Nrf2, *Salvia rosmarinus* extracts also exert a direct influence on endogenous antioxidant enzymes. In oral squamous cell carcinoma (OSCC) cells, it was observed

a significant increase in superoxide dismutase (SOD) activity, accompanied by decreased MDA levels, indicating successful restoration of cellular redox equilibrium [61].

2.2. In Vitro Experimental Evidence

Experimental evidence indicates that *Salvia rosmarinus* extracts exhibit antioxidant activity across several cell lines. In OSCC cells, *Salvia rosmarinus* treatment increased SOD activity and reduced MDA levels after 72 h. These effects were associated with reduced cell viability and clonogenic capacity, as well as inhibition of the FOXD1/mTOR pathway, underscoring the relationship between antioxidant activity and antiproliferative effects [61]. Research summarized by Petiwala and Johnson [17] indicated that carnosic acid and carnosol increase GSH levels, inhibit inflammatory mediators such as COX-2 and iNOS, and enhance Nrf2-mediated antioxidant pathways in tumor cells.

Throughout the manuscript, identify the tested material as (i) chemically characterized whole-plant extract, (ii) essential oil, (iii) enriched fraction, or (iv) isolated compound. For example: "Isolated carnosic acid decreased viability and activated apoptosis-related markers in HepG2 cells. This observation cannot be attributed to uncharacterized whole-rosemary extracts [18]. Molecular docking simulations suggest that the secondary metabolites 1,8-cineole, α-pinene, and camphor act together and exhibit high thermodynamic affinity for key cancer therapeutic targets, including estrogen receptor alpha (ERα), B-Raf kinase, and protein kinase B (AKT1). Findings indicate that essential oil may be a promising phytotherapeutic agent with notable specificity for malignant tissues. Other studies have also shown that rosmarinic acid restores and activates the p53 tumor suppressor protein, tumor necrosis factor alpha (TNF-α), and nuclear factor kappa B (NF-κB). The activation modulates Bcl-2 family proteins by upregulating pro-apoptotic Bax and downregulating anti-apoptotic Bcl-2, thereby inducing caspase-3 activation and apoptosis in cancer cells while significantly enhancing the efficacy of Paclitaxel [60,62].

2.3. Experimental Evidence In Vivo

Animal studies indicate that extracts of *Salvia rosmarinus* exert systemic antioxidant effects. Moore et al. [18] found that carnosic acid-rich extracts increased glutathione (GSH) levels and reduced lipid peroxidation in the liver, skin, and other tissues exposed to carcinogens throughout an increased expression of Nrf2-regulated antioxidant proteins, including HO^{-1}, as well as other defense genes. Petiwala and Johnson [16] reported that carnosic acid reduced oxidative damage and tumor progression in animal models of skin, bowel, and prostate cancers, as well as leukemia, through the regulation of antioxidant and anti-inflammatory pathways.

2.4. Comparison Between Extracts and Isolated Compounds

The antioxidant activity of *Salvia rosmarinus* is determined by its phytochemical composition. Methanolic, ethanolic, and supercritical CO_2 extracts contain high concentrations of carnosic acid, carnosol, and rosmarinic acid, whereas essential oils consist primarily of volatile monoterpenes. These chemical differences influence antioxidant efficacy across various models [24,63]. Evidence indicates that whole extracts may exhibit greater biological activity than isolated compounds; likely, due to additive or complementary interactions among phenolic diterpenes, flavonoids, and other metabolites, as formal quantitative combination analyses are required to confirm true pharmacological synergy. Nevertheless, carnosic acid and carnosol remain the principal agents responsible for the antioxidant and cytoprotective effects of *Salvia rosmarinus* [17,64,65].

Rosmarinic acid (RA) enhances the cytotoxic effects of doxorubicin (DOX) in both two-dimensional (2D) and three-dimensional (3D) breast cancer models, while exhibiting

minimal toxicity to normal cells. The combination induces apoptotic cell death through G2/M-phase arrest, mitochondrial depolarization, and increased reactive oxygen species (ROS) levels, thereby disrupting tumor spheroid integrity [66]. In ovarian adenocarcinoma, RA enhances the efficacy of DOX by inhibiting proliferation, migration, and invasion, promoting apoptosis, and improving chemosensitivity. RA also suppresses MDR1 transcription by downregulating P-glycoprotein (P-gp), thereby partially reversing multidrug resistance in DOX-resistant cancer cells [67–69].

2.5. The Anticancer Properties of Salvia rosmarinus Extracts

To ensure pharmacological precision across this review, a strict distinction must be maintained among the different *Salvia rosmarinus* preparations evaluated in the literature: whole crude extracts (aqueous, hydroalcoholic, or organic), volatile essential oils, chemically enriched fractions, and isolated single phytochemicals (such as pure carnosic acid, carnosol, or rosmarinic acid). Because extraction polarity and processing fundamentally dictate the final metabolite profile, the bioactivity observed for an isolated compound—often tested at high, purified micromolar concentrations—cannot be automatically extrapolated to whole crude extracts or essential oils without direct comparative evidence. Consequently, throughout the following mechanistic sections, each biological effect is attributed strictly to the specific preparation or single constituent tested in the corresponding primary study.

Scientific evidence indicates that *Salvia rosmarinus* exhibits a broad range of anticancer properties, as demonstrated in various preclinical models, including human tumor cell lines and animal carcinogenesis models. These effects are primarily associated with phenolic diterpenes, such as carnosic acid and carnosol, as well as other bioactive compounds found in whole *Salvia rosmarinus* extracts. These metabolites affect key processes involved in tumor progression, including cell proliferation, apoptosis, inflammation, oxidative stress, angiogenesis, and intracellular signaling pathways such as PI3K/Akt/mTOR, NF-κB, and Nrf2 [17,21].

Additionally, some studies have reported chemosensitizing effects when *Salvia rosmarinus* extracts are combined with conventional antineoplastic agents, suggesting a potential role as therapeutic adjuvants [19]. Interpretation of these findings requires consideration of extract heterogeneity, phytochemical composition, dosage, and experimental models. Table 2 presents a standardized summary of evidence regarding the anticancer activity of *Salvia rosmarinus*, including methodological details to support accurate interpretation and prevent the misapplication of findings from review articles or specific models.

2.6. Molecular Mechanisms Involved in Anticancer Activity

Salvia rosmarinus exhibits anticancer effects by influencing multiple pathways that support tumor survival, growth, and progression. Compounds such as carnosic acid, carnosol, and rosmanol induce apoptosis, regulate the cell cycle, reduce oxidative stress, and modulate inflammatory and immune responses. The multi-target approach in herbal medicine enables simultaneous action on diverse cancer-related processes [17,21].

2.6.1. Induction of Apoptosis

Induction of apoptosis is a key antitumor mechanism of compounds derived from *Salvia rosmarinus*. The extract significantly reduced cell viability and increased caspase-3 activity in oral squamous cell carcinoma (OSCC), indicating the activation of apoptotic pathways associated with the suppression of FOXD1 and mTOR [61]. Carnosic acid induced apoptosis in both multidrug-sensitive and multidrug-resistant leukemia cell lines by increasing p53 levels, reducing FAK levels, and promoting PARP cleavage, thereby activating programmed cell death pathways [70]. Similarly, rosmanol induced dose-dependent apop-

tosis in CNE2 nasopharyngeal carcinoma cells, as evidenced by chromatin condensation, nuclear fragmentation, loss of mitochondrial potential, and increased levels of pro-apoptotic proteins [71].

Table 2. Anticancer evidence of *Salvia rosmarinus* extracts or bioactive metabolites in in vitro assays.

Cancer Model	Extract/Compound	Homologous Experimental Model	Biological Effect	Main Results	Experimental Evidence
Breast cancer	Crude extract	MCF-7 and MDA-MB-231 cell lines	Cell proliferation, apoptosis, cellular migration, ROS	Antiproliferative activity, induction of apoptosis, and inhibition of cell migration, with lower toxicity towards non-tumor cells	Original experimental study. The results pertain specifically to methanolic extracts from leaves originating in Italy [70].
Squamous cells oral carcinoma (OSCC)	Crude extract	Human cell line (OSCC)	MTT, CFU, SOD, MDA, caspase-3, FOXD1, mTOR, LC3-I/LC3-II	Significant decrease in cell viability and colony formation; increase in SOD; decrease in MDA; inhibition of FOXD1/mTOR and modulation of autophagy	The results directly correspond to the reference. The antioxidant and antiproliferative effects were measured experimentally in a single-cell model [27].
Head and neck cancer	Crude extract	Cell line HEp-2	Cytotoxicity, molecular interactions with COX-2	Cytotoxic effect associated with COX-2 modulation	Evidence supports cytotoxic activity and potential COX-2 interaction; do not infer mechanisms the authors did not report [39].
Comparison between complete extracts and isolated compounds	Crude extract, carnosic and rosmarinic acids	Diverse cell and animal models	Cell survival, apoptosis, tumor growth, oxidative stress	Complete extracts and isolated compounds showed significant anticancer activity	Evidence suggests crud extracts may act synergistically but does not show superiority to isolated compounds [17,21].

2.6.2. Cell-Cycle Arrest

Metabolites can disrupt cell-cycle progression, another crucial aspect of their anticancer effects. Rosmanol notably decreased levels of cyclin D1, CDK4, CDK6, and phosphorylated retinoblastoma protein (pRB), thereby hindering the G1/S transition and reducing CNE2 cell proliferation [71]. Carnosic acid and carnosol induced cell-cycle arrest at different phases (G0/G1, S, and G2/M) across various tumor models, leading to decreased cell growth and increased apoptosis [17].

2.7. PI3K/Akt/mTOR Modulation

The PI3K/Akt/mTOR pathway regulates cell survival, tumor growth, and resistance.

Salvia rosmarinus extract reduces mTOR and FOXD1 expression in OSCC cells, affects autophagy-related proteins, and decreases cell proliferation [61]. Where carnosic acid and carnosol modulated this pathway, inhibiting proliferation and promoting apoptosis in cancer models [17].

2.8. Regulation of MAPK

Mitogen-activated protein kinases (MAPKs) play essential roles in cell proliferation, differentiation, and apoptosis. In IMR-32 cells, carnosic acid activated p38, ERK1/2, and JNK1, which was associated with increased apoptosis and caspase activation. Partial inhibition of p38 attenuated these effects, confirming its role in the antitumor response [72]. Rosmanol, a biocative metabolite of rosemary, reduced levels of proteins associated with the JNK, ERK, and p38 MAPK pathways in CNE2 cells, indicating that MAPK regulation varies by compound and tumor context [71].

2.9. Inhibition of NF-κB

The NF-κB pathway plays a critical role in inflammation, cell growth, and drug resistance. Rosmanol reduced NF-κB and TNF-α levels in CNE2 cells, thereby inhibiting cell growth and promoting apoptosis [71], whereas carnosic acid and carnosol reduced inflammatory mediators, including COX-2 and iNOS, in various tumor models by inhibiting the NF-κB pathway [17].

2.10. Epigenetic Modulation

Evidence on epigenetic mechanisms remains limited. Transcriptomic and bioinformatic analyses was applied to identify genes associated with sensitivity or resistance to carnosic acid, including TP53, EGFR, ABCB1, ABCG2, and ABCB5, which are involved in cell survival and drug resistance [62]. As the studies did not directly assess epigenetic modifications, such as DNA methylation, histone modifications, or microRNA regulation, it is not possible to determine definitively which epigenetic mechanisms are associated with *Salvia rosmarinus* extracts.

2.11. Inhibition of Angiogenesis

Studies have demonstrated a notable reduction in tumor growth in animal models treated with carnosic acid and *Salvia rosmarinus* extracts. It was reported that rosemary reduced tumor size in skin, bowel, prostate, and leukemia models, suggesting a potential indirect effect on tumor angiogenesis. However, because the studies did not directly measure angiogenic markers such as VEGF, CD31, or microvascular density, the evidence does not definitively establish a specific anti-angiogenic mechanism [17].

2.12. Regulation of the Immune Response

In addition to affecting tumor cells, compounds derived from *Salvia rosmarinus* may also influence the immune response. Fewer regulatory T cells (Tregs) and higher interferon-gamma (IFN-γ) levels were reported in animals treated with carnosic acid, suggesting enhanced antitumor immunity [17]. These findings indicate that the anticancer effects of *Salvia rosmarinus* may involve immunomodulatory mechanisms in addition to antioxidant, anti-inflammatory, and pro-apoptotic actions. However, further research is needed to identify the specific cells and immune mediators involved [17,21] Figure 1.

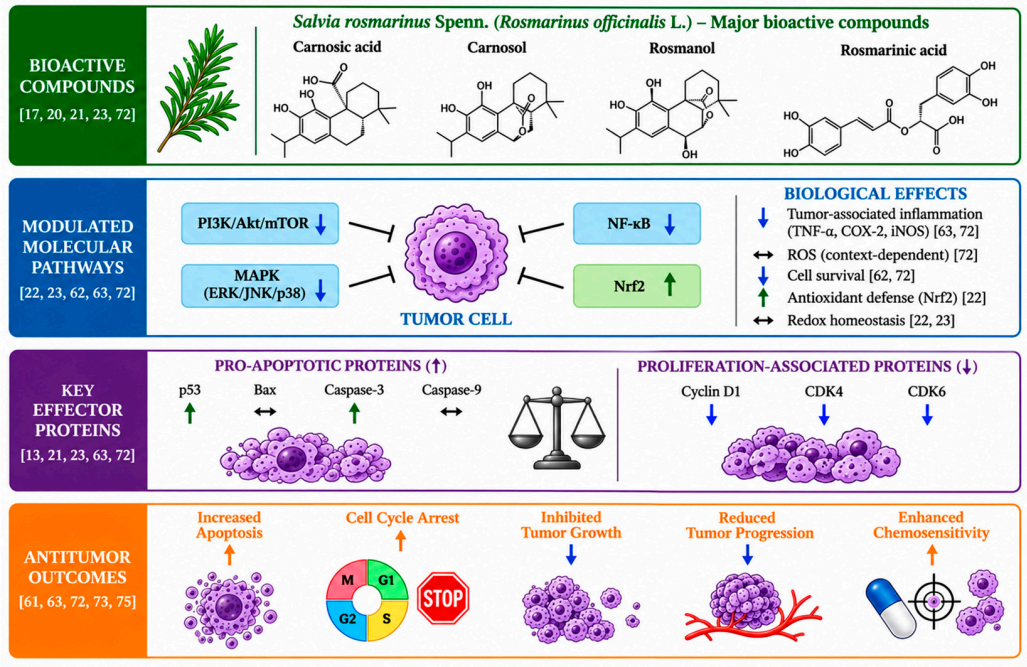


Figure 1. Molecular pathways involved in anticancer activity of *Salvia rosmarinus* extracts and bioactive metabolites.

3. Discussion

A rigorous assessment of the translational potential of *Salvia rosmarinus* in integrative oncology requires a clear distinction among findings from in vitro models, in vivo animal experiments, and clinical research. Most mechanistic evidence currently comes from in vitro platforms, which enable the precise mapping of intracellular signaling pathways and assessments of apoptosis and cell-cycle arrest in human tumor cell lines. However, these systems do not reproduce the complexity of living organisms, and their findings must be corroborated by in vivo experiments. Animal models provide essential data on systemic pharmacokinetics, tumor-mass reduction, modulation of the antitumor immune response, and toxicity in vital organs. Clinical research represents the highest level of evidence; nevertheless, evidence concerning rosemary remains extremely limited, and large-scale randomized trials are lacking. Clearly delineating the scope and limitations of these three levels of research is essential to prevent the premature extrapolation of laboratory findings to clinical practice.

3.1. Relationship Between Antioxidant Activity and Anticancer Activity

The relationship between antioxidant activity and anticancer effects represents a key mechanism underlying the biological potential of *Salvia rosmarinus*. The plant contains phenolic diterpenes and terpenoids, including carnosic acid, carnosol, ursolic acid, and rosmarinic acid, which scavenge free radicals and reduce oxidative stress by neutralizing reactive oxygen species (ROS), which may protect cells from oxidative damage that could contribute to cancer development [24,73].

Experimental cancer models support an association in human OSCC cells, where *Salvia rosmarinus* extract reduced malondialdehyde (MDA), a marker of lipid peroxidation, and increased superoxide dismutase (SOD) activity. These antioxidant effects were associated with reduced cell viability, suppression of FOXD1/mTOR signaling, and induction of apoptosis, thereby linking oxidative stress regulation to antiproliferative effects [61]. Studies of human tumor cell lines have demonstrated that ethanolic extracts rich in phe-

nolics and flavonoids exert stronger anticancer effects, suggesting that their antioxidant properties may contribute to tumor growth suppression, underscoring the relationship between phytochemicals and biological activity [26].

Compounds derived from *Salvia rosmarinus*, including carnosic acid and carnosol, modulate redox-sensitive pathways such as NF-κB, PI3K/Akt/mTOR, and Nrf2 to reduce inflammation, enhance antioxidant levels, and promote cancer cell death. Their antioxidant activity also helps regulate signaling networks involved in cancer growth [16]. A review of preclinical studies found that *Salvia rosmarinus* extracts reduce oxidative stress markers and promote cell-cycle arrest and apoptosis in various cancers, including breast, colon, prostate, lung, and liver cancers. The antioxidant effects of *Salvia rosmarinus* are suggested to maintain cellular redox balance, potentially disrupting pathways essential for tumor growth [18]. Evidence indicates that the antioxidant and anticancer effects of *Salvia rosmarinus* are interconnected. Its phytochemicals influence tumor growth, survival, inflammation, and cell death by regulating oxidative stress, a key biological pathway. A dual role highlights *Salvia rosmarinus's* potential for combined cancer prevention and treatment.

Research on *Salvia rosmarinus* and its bioactive components has long played a significant role in oncological and translational medicine, making it one of the most extensively studied botanicals for complementary strategies [19]. The scientific literature has investigated how the complex whole-plant matrix and essential oils modulate the tumor microenvironment through multiple targets. The combined presence of phenolic diterpenes, organic acids, and volatile monoterpenes produces synergistic effects that disrupt several "hallmarks of cancer." These interactions may help reduce oxidative and inflammatory stress during early carcinogenesis and increase the sensitivity of malignant cells to standard chemotherapy [13].

Substantial evidence supports the potential use of standardized rosemary extracts as adjuvant agents in antineoplastic therapy [19]. Systematic reviews indicate that rosemary's phytochemical heterogeneity, which is influenced by extraction methods and solvent polarity, determines its biological activity [13]. Polyphenol-rich extracts interfere with signaling pathways essential for cell survival, resulting in cell-cycle arrest and apoptosis in solid tumor models, including breast, colon, and prostate cancers. The literature underscores the importance of standardizing these extracts to translate preclinical findings into reproducible and safe clinical applications.

Recent advances have enhanced our understanding of the antitumor effects of compounds derived from *Salvia rosmarinus*, particularly their roles in regulating energy metabolism and cellular homeostasis. Studies have elucidated how carnosic acid acts in lung cancer models, showing that this phenolic diterpene activates the Sestrin-2/LKB1/AMPK signaling pathway [74,75]. This pathway acts as a metabolic stress sensor, limiting uncontrolled proliferation and inducing targeted autophagy in tumor cells. A relationship among adaptive stress responses, energy regulation, and programmed cell death highlights a specific therapeutic target that complements established pathways, including mTOR and NF-κB.

In summary, integrating historical evidence from large-scale studies with recent mechanistic findings underscores the multifactorial role of *Salvia rosmarinus* in integrative oncology [13,74]. The shift from neutralizing reactive oxygen species (ROS) to modulating transcriptional switches and autophagy cascades demonstrates that rosemary functions as a complex epigenetic and metabolic modulator rather than merely as an antioxidant. The analysis addresses methodological inconsistencies across individual studies and refines future research priorities, emphasizing the development of nanoformulations and the conduct of controlled clinical trials as essential next steps for this botanical species Figure 2.

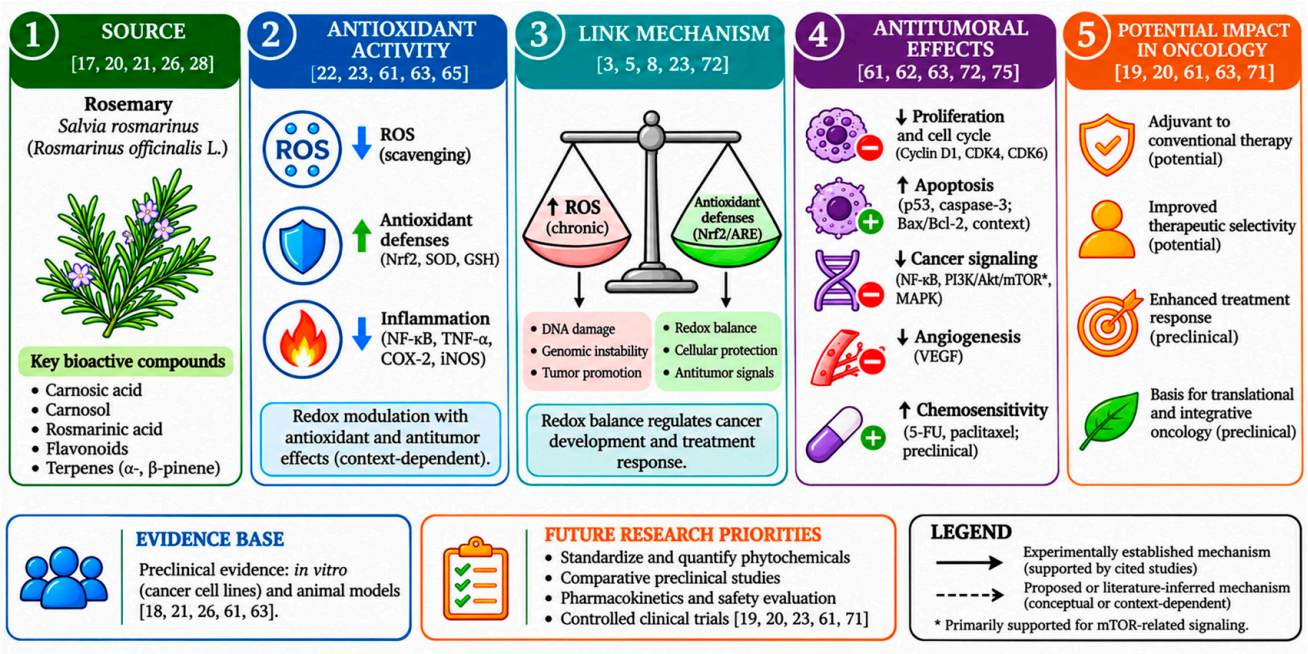


Figure 2. Conceptual model that integrates antioxidant activity and antitumor effects of *Salvia rosmarinus* extracts and bioactive metabolites.

3.2. Translational Potential and Therapeutic Uses

3.2.1. Chemopreventive Agent

Evidence suggests that *Salvia rosmarinus* has chemopreventive potential through its effects on early carcinogenesis. Key constituents, including carnosic acid, carnosol, and rosmarinic acid, exhibit antioxidant and anti-inflammatory properties that may mitigate oxidative stress and protect DNA from damage caused by ROS. Because persistent oxidative stress and inflammation can contribute to tumor initiation and progression, the capacity of *Salvia rosmarinus* compounds to restore redox homeostasis may help reduce cancer risk [17,21,24]. Phytochemicals in *Salvia rosmarinus* also exert antioxidant effects and modulate molecular pathways, including NF-κB, PI3K/Akt/mTOR, and MAPK, while activating Nrf2 responses. These effects may create a less favorable cellular environment for cancer development, supporting the potential of *Salvia rosmarinus* as a natural chemopreventive agent, particularly for individuals experiencing chronic inflammation or oxidative stress [17,61].

3.2.2. Adjuvant to Chemotherapy

Interest in the therapeutic use of *Salvia rosmarinus* extracts for cancer treatment is increasing. Preclinical research indicates that these compounds may enhance therapeutic efficacy by increasing tumor cells' sensitivity to drugs and modulating oxidative and inflammatory pathways associated with treatment resistance. A multitargeted approach is important given the complexity of cancer signaling networks [21,70].

Salvia rosmarinus extracts promote apoptosis by increasing levels of p53, Bax, caspase-3, and caspase-9, and inhibiting proliferation-related proteins such as Cyclin D1, CDK4, and CDK6. These effects may enhance chemotherapy efficacy and reduce required doses, but clinical trials are needed to confirm them [17,71].

3.2.3. Synergy with Antineoplastic Drugs

Several studies indicate that compounds found in *Salvia rosmarinus*, including carnosic acid and carnosol, may enhance the efficacy of cancer treatments such as 5-fluorouracil, cisplatin, paclitaxel, and tamoxifen. These compounds may promote apoptosis, inhibit

growth signaling, reduce inflammation, modulate oxidative stress, and increase cancer cell sensitivity [17,21]. By targeting multiple pathways, *Salvia rosmarinus* compounds may also help overcome cancer drug resistance by disrupting NF-κB, PI3K/Akt/mTOR, and STAT3 signaling [21,71], which could enhance antitumor effects and reduce chemotherapy-induced survival responses. Further research, including clinical trials, is required to confirm their potential in humans.

When evaluating *Salvia rosmarinus*, note that greater biological activity in a crude extract than in an individual compound does not, by itself, establish pharmacological synergy. The effectiveness of whole-plant extracts may arise from additive effects or from multiple metabolites acting on distinct biological targets. Demonstrating true synergy requires direct experimental evidence and rigorous mathematical analysis, such as isobologram analysis or calculation of the Combination Index (CI). The literature indicates that the extent of these interactions and the resulting biological activity depend on agronomic and technological factors. For example, the extraction method—such as using ethanol rather than hexane—and the plant part selected, primarily the leaves, can significantly influence the phytochemical profile. Hexane extracts concentrate lipophilic diterpenes, such as carnosic acid and carnosol, thereby producing a cytotoxicity profile that differs from that of aqueous extracts rich in rosmarinic acid. Accordingly, claims of synergy among rosemary components, or rosemary and chemotherapeutic agents such as 5-fluorouracil or cisplatin, should be interpreted cautiously. Reproducibility depends on standardizing both chemical composition and extraction methods.

3.3. Safety and Toxicity Considerations

Current evidence indicates that *Salvia rosmarinus* extracts are generally safe in preclinical studies and exhibit limited toxicity at anticancer concentrations. These findings have increased interest in *Salvia rosmarinus* as a complementary therapy. However, variations in extraction methods, phytochemical composition, and dosage hinder the development of standardized safety guidelines [21,64]. Although the toxicological data are promising, substantial gaps remain in our understanding of long-term safety, pharmacokinetics, bioavailability, and interactions with anticancer treatments. The absence of clinical trials also limits the ability to determine therapeutic windows and assess long-term use in patients with cancer. Future research should prioritize comprehensive toxicological studies and well-controlled clinical trials to support the safe integration of *Salvia rosmarinus*-based products into cancer therapies [21,65].

3.4. Limitations of the Available Evidence

Although evidence supporting the antioxidant and anticancer effects of *Salvia rosmarinus* is growing, these findings should be interpreted cautiously given several methodological limitations in the reviewed studies. A principal limitation is the considerable heterogeneity among the extracts examined. The studies used aqueous, ethanolic, methanolic, hexane, hydroalcoholic, and supercritical extracts, as well as fractions enriched in compounds such as carnosic acid, carnosol, rosmanol, and rosmarinic acid. The diversity complicates direct comparisons because phytochemical composition varies with solvent, extraction method, and processing conditions. Furthermore, some studies investigated whole extracts, whereas others examined purified compounds, making it difficult to establish the effects of the complete plant matrix [17,21,64].

The reviewed studies employ a range of experimental models, dosages, durations, biomarkers, and methodologies. Most of the evidence is derived from in vitro investigations using various cancer cell lines, while animal studies remain limited. Heterogeneity precludes quantitative comparisons and constrains a comprehensive understanding of dose–

response relationships. Furthermore, molecular mechanisms were not assessed consistently, resulting in differences in the depth of biological analysis. The chemical composition of *Salvia rosmarinus* varies considerably according to agronomic, environmental, and technological factors, including geographic origin, plant part, and extraction method. Hexane extracts primarily contain diterpenes and lipophilic terpenes, including carnosic acid, carnosol, rosmanol, α-pinene, β-pinene, and ursolic acid. Ethanolic and aqueous extracts generally contain higher concentrations of phenolic compounds and flavonoids, such as rosmarinic acid, caffeic acid, luteolin, hesperidin, apigenin, and quercetin [24–28]. Many studies do not provide detailed quantitative phytochemical analyses or standardization, thereby limiting reproducibility and complicating comparisons.

Beyond sample heterogeneity, claims regarding rosemary's potential as a therapeutic adjuvant, including its ability to enhance chemotherapy or reduce drug-induced toxicity, should be interpreted with caution due to limitations in current preclinical evidence. A significant gap in the literature is the absence of robust data on the in vivo pharmacokinetics and bioavailability of compounds such as carnosic acid and carnosol. The inhibitory concentrations (IC_{50}) observed in vitro, typically 6–75 μM, are difficult to achieve in human tissues through standard oral or systemic administration because of rapid metabolism, low absorption, and fast clearance. Additionally, the lack of long-term studies prevents the establishment of a comprehensive safety and chronic toxicity profile, which is necessary for extended oncological treatments. The risk of herb–drug interactions also remains unresolved. By affecting common metabolic pathways or cellular transporters, such as ABC glycoproteins identified through bioinformatic analysis, *Salvia rosmarinus* extracts could unpredictably alter plasma concentrations of chemotherapeutic agents, potentially reducing efficacy or increasing toxicity.

3.5. Perspectives: Implications for Future Research

Although *Salvia rosmarinus* has demonstrated promising anticancer effects in preclinical investigations, significant limitations remain. Most of the available evidence is derived from in vitro and animal models, and no high-quality randomized clinical trials have confirmed its safety or efficacy in patients with cancer. Accordingly, the translation of these experimental findings into clinical practice remains substantially limited. Future research should standardize extraction methods, characterize phytochemicals using chromatographic and spectrometric techniques, establish quality-control standards, and quantify key bioactive compounds, including carnosic acid, carnosol, and rosmarinic acid, to enhance reproducibility and comparability. Further studies are also needed to elucidate the anticancer mechanisms of *Salvia rosmarinus*, particularly its effects on pathways involved in apoptosis, oxidative stress, inflammation, and cell growth. Comparisons of whole extracts with isolated compounds may reveal synergistic effects and help identify the most effective formulations.

Further research on pharmacokinetics, pharmacodynamics, and long-term toxicology is needed to determine safe dosages, safety, and drug–herb interactions. Innovative delivery methods, such as nanoformulations, could improve bioavailability and effectiveness. Well-designed clinical trials are essential to evaluate *Salvia rosmarinus* potential as a complementary cancer treatment. Strong clinical evidence is key to integrating it into evidence-based, integrative care.

4. Methods

A structured literature search was conducted in the PubMed database to identify biomedical, pharmacological, and phytochemical investigations evaluating *Salvia rosmarinus* extracts, their secondary metabolites, and their activity in cancer. The search covered all

records from database inception from January 3rd up to December 2025, using the following complete Boolean search strategy: "*Salvia rosmarinus*" (Title/Abstract) OR "*Rosmarinus officinalis*" (Title/Abstract) OR "rosemary extract" (Title/Abstract) AND "antioxidant" (Title/Abstract) OR "oxidative stress" (Title/Abstract) AND "anticancer" (Title/Abstract) OR "antitumor" (Title/Abstract) OR "cancer" (Title/Abstract).

The initial search retrieved a total of 52 records. After removing 5 duplicate records, the titles and abstracts of 47 unique publications were screened. From this pool, 14 articles were excluded for not meeting the eligibility criteria: 7 did not directly evaluate antioxidant or anticancer activity, 3 were conference abstracts without full text or brief reports lacking experimental data, and 4 lacked phytochemical characterization or were written in languages other than English.

Following this systematic screening process, 33 core publications were selected to form the experimental and phytochemical foundation of this review (summarized in Tables 1 and 2). Additionally, to provide epidemiological context on cancer, explain the biochemical basis of oxidative stress, and contextualize the molecular pathways and historical reviews recommended during peer review, 42 complementary references were incorporated through targeted manual searching, bringing the total to 75 references cited throughout the manuscript.

A literature search was conducted in PubMed to identify studies reporting biomedical, pharmacological, and phytochemical investigations of *Salvia rosmarinus* extracts and their natural products in relation to cancer. The following search terms were used to refine the search: *Rosmarinus officinalis*, *Salvia rosmarinus*, carnosic acid, carnosol, rosmarinic acid, oxidative damage, anticancer effects, and molecular mechanisms. The approach enabled the retrieval of manuscripts examining the antioxidant and anticancer properties of *Salvia rosmarinus* extracts and their principal bioactive constituents.

Manuscripts in English were included regardless of publication year. The search identified in vitro and in vivo experiments, phytochemical studies, mechanistic research, and scientific reviews that expose *Salvia rosmarinus* chemical composition, biological effects, and underlying mechanisms. The search also included publications on secondary metabolites such as carnosic acid, carnosol, rosmarinic acid, ursolic acid, flavonoids, and terpenes, as well as their roles in oxidative stress, cell proliferation, apoptosis, inflammation, and cancer. The inclusion criteria included in vitro studies on the antioxidant/anticancer properties of *Salvia rosmarinus* extracts; in vivo animal studies; phytochemical research identifying secondary metabolites; mechanistic investigations of molecular pathways; and relevant scientific reviews for context. Only the papers written in English language were considered. Publications as well as duplicates, conference abstracts without full text, brief reports with limited information, and studies lacking experimental results or phytochemical data on *Salvia rosmarinus* were excluded.

A standardized data extraction was conducted for each publication, recording variables such as *Salvia rosmarinus* extract type, preparation method, plant part, origin region, model, sample size, procedures, responses, and results (Table 1) to allow for comparison of methodologies, identification of metabolites associated with activity, and analyses of antioxidant and anticancer evidence for *Salvia rosmarinus*.

5. Conclusions

Current evidence suggests that *Salvia rosmarinus* is a promising source of bioactive compounds with antioxidant and anticancer properties. A comprehensive review of the literature corroborates findings from both in vitro and in vivo studies, highlighting the effects of *Salvia rosmarinus* extracts—particularly carnosic acid, carnosol, and rosmarinic acid—on pathways involved in tumor development. Nevertheless, most of the evidence

remains preclinical, and the lack of robust clinical data substantially limits the extrapolation of favorable findings to cancer chemotherapy.

Key mechanisms include the reduction of oxidative stress through the scavenging of reactive oxygen species and the enhancement of endogenous antioxidant defenses, alongside the modulation of signaling pathways such as NF-κB, PI3K/Akt/mTOR, MAPK, STAT3, and Nrf2. These effects contribute to increased apoptosis, cell-cycle arrest, reduced proliferation and inflammation, and slower tumor growth. While redox modulation is closely intertwined with tumor biology, these effects are strictly context- and concentration-dependent; consequently, antioxidant activity alone does not directly establish anticancer efficacy. Rather, *Salvia rosmarinus* constituents exert their antineoplastic actions through pleiotropic, redox-sensitive, and antioxidant-independent signaling mechanisms that selectively disrupt malignant cell survival.

As a source of natural compounds, *Salvia rosmarinus* shows potential in cancer prevention and as an adjunctive therapy. Experimental findings suggest that certain rosemary preparations may enhance the efficacy of chemotherapy; however, rigorous mathematical and experimental protocols are necessary to formally confirm synergistic interactions. Future research must standardize extraction methods, characterize phytochemical constituents across variable plant parts, conduct deeper preclinical investigations, and thoroughly assess pharmacokinetics, drug–herb interactions, and long-term toxicity. Ultimately, meticulously designed randomized clinical trials are indispensable to determine whether products derived from *Salvia rosmarinus* can be integrated safely and effectively into evidence-based oncology practice.

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Abbreviations

The following abbreviations are used in this manuscript:

5-FU	5-Fluorouracil
ABCB1	ATP-Binding Cassette subfamily B member 1
ABCB5	ATP-Binding Cassette subfamily B member 5
ABCG2	ATP-Binding Cassette subfamily G member 2

Akt	Protein kinase B
AP-1	Activator Protein 1
AR	Androgen Receptor
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
CCSA-4	Colon Cancer-Specific Antigen 4
CD31	Cluster of differentiation 31
CDK4	Cyclin-Dependent Kinase 4
CDK6	Cyclin-Dependent Kinase 6
CEA	Carcinoembryonic Antigen
COX-2	Cyclooxygenase-2
DNA	Deoxyribonucleic Acid
EGFR	Epidermal Growth Factor Receptor
ER	Endoplasmic Reticulum
ERK1/2	Extracellular signal-Regulated Kinases 1 and 2
ERα	Estrogen Receptor alpha
FAK	Focal Adhesion Kinase
FDA	Food and Drug Administration
FOXD1	Forkhead Box D1
GSH	Reduced glutathione
H_2O_2	Hydrogen peroxide
HO•	Hydroxyl
IC_{50}	Half-maximal Inhibitory Concentration
IFN-γ	Higher interferon-gamma
iNOS	Inducible Nitric Oxide Synthase
JNK1	c-Jun N-terminal Kinase 1
LC3-I/LC3-II	Microtubule-associated protein 1 Light Chain 3, forms I and II
MAPKs	Mitogen-Activated Protein Kinases
MDA	Malondialdehyde
miR-15b	MicroRNA-15b
mTOR	Mechanistic Target Of Rapamycin
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NF-κB	Nuclear Factor kappa B
Nrf2	Nuclear factor erythroid 2-related factor 2
O_2^-	Superoxide
OSCC	Oral Squamous Cell
PARP	Poly(ADP-ribose) Polymerase
pBR	Phosphorylated Retinoblastoma Protein
PI3K	Phosphoinositide 3-Kinase
PSA	Prostate-Specific Antigen
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SOD	Superoxide Dismutase
STAT3	Signal Transducer and Activator of Transcription 3
TNF-α	Tumor Necrosis Factor alpha
TP53	Tumor Protein p53
Tregs	Regulatory T cells
VEGF	Vascular Endothelial Growth Factor
Sestrin-2	SESN2 is regarded as a stress-induced protein
MRP2	Multidrug Resistance-Associated Protein 2
K562	Leukemia cell line
HO-1	Hemooxigenasa 1
CNE2	Nasopharyngeal carcinoma cells
cyclin D1	Protein that controls the transition from G1 to S phase in the cell cycle
IMR-32	Human neuroblastoma cell line
P38	p38 Mitogen-Activated Protein Kinase
CDK4,	Cyclin-Dependent Kinases 4
CDK6	Cyclin-Dependent Kinases 6
JNK	Jun N-terminal Kinase
ERK	Extracellular Signal-Regulated Kinase
MCF-7	Human breast cancer cell line
MDA-MB-231	Triple-Negative Breast Cancer
PC3	Androgen-independent prostate cancer cell line
LNCaP	Androgen-dependent prostate cancer cell line
HT29	Colorectal adenocarcinoma cell line

HCT116	Colon carcinoma cell line
HL-60	Acute promyelocytic leukemia cell line
CFU	Colony-Forming Unit

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