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REVIEW ARTICLE

Exploring the Therapeutic Potential of *Rosmarinus officinalis*: A Review Study

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Abstract

Herbal remedies have long been esteemed for their substantial contribution to human health. The healthcare sector is increasingly acknowledging the significance of various herbs and plants, leading to a surge in their global popularity. This resurgence in interest is spurring a closer examination of their potential benefits in the creation of new drugs. The unique compounds found in these plants are seen as valuable sources for meeting different pharmacological objectives, inspired by their historical usage in folk medicine. The purpose of this review was to thoroughly review current research on *Rosmarinus officinalis* L., with the aim of uncovering the key chemicals and biological effects linked to this herb. Evidence from various studies highlights the medicinal potential of specific compounds such as carnosol, rosmarinic acid, and carnosic acid in addition to the plant extracts and essential oils. This paper explores the most frequently observed effects related to *R. officinalis* and its components. Understanding the medicinal uses of these plants can have implications that extend beyond herbal therapy, reaching into the field of pharmacological research. Given the properties of this herb, further human studies are essential to evaluate its potential for developing versatile medicines suitable for clinical application.

Major Findings: *Rosmarinus officinalis* exhibits significant anticancer, antioxidant, antimicrobial, antidiabetic, and neuroprotective properties. Key compounds like carnosic acid, rosmarinic acid, and carnosol contribute to these effects, highlighting the plant's potential for developing versatile therapeutic applications.

Keywords: Anticancer, Antimicrobial, Herbal Medicine, Metabolic Disorders, Neuroprotection, *Rosmarinus officinalis*

Abbreviations: AChE: Acetylcholinesterase, AD: Alzheimer's disease, ALT: Alanine transaminase, AST: Aspartate transaminase, BChE: Butyrylcholinesterase, BHA: Butylated hydroxyanisole, BHT: Butylated hydroxytoluene, CA: carnosic acid, CRC: Colorectal cancer cells, HSCs: hepatic stellate cells, MDA: Malondialdehyde, RA: Rosmarinic acid, TC: Total cholesterol, TG: Triglyceride.

1. Introduction

The exploration of medicinal plants and their bioactive compounds is vital for developing novel therapeutic approaches to treat and prevent diverse diseases[1,2]. These plants are celebrated for their abundance of natural substances that demonstrate powerful biological impacts, including but not limited to anticancer, anti-inflammatory, antioxidant, brain, memory, antimicrobial, antidiabetic, and antihyperlipidemic effects[3-6]. Among these, *R. officinalis*, a distinguished herb in the Lamiaceae family, has garnered substantial interest due to its therapeutic attributes[7]. Originally from the Mediterranean, *R. officinalis* has a long history of use in various medicinal applications and is now cultivated worldwide. It has been utilized as an antibacterial agent

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and a treatment for rheumatism, bloating, and minor cuts, in addition to managing fevers, indigestion, and problems related to circulation and the kidneys. The essential oil and extracts from the plant's leaves and flowers are recognized for their capacity to act as expectorants, and diuretics, and to alleviate spasms[8,9]. Extensive research on *R. officinalis* extracts has revealed their wide-ranging biological activities, including anticarcinogenic[10], antioxidant, and hepatoprotective properties[11], along with antimicrobial[12] and anti-inflammatory capabilities[13], and their effectiveness in diabetes management[14]. The plant has also been studied for its neuroprotective benefits and its impact on brain function and memory[15]. This research article offers a detailed review of the studies focused on the therapeutic possibilities of *R. officinalis*, with particular attention to its anticancer, antioxidant, antimicrobial, antidiabetic, antihyperlipidemic, and neuroprotective and memory-enhancing effects (Figure 1). By thoroughly examining existing literature, this study aims to illuminate the pharmacological properties of *R. officinalis* and explore its potential applications across diverse therapeutic fields.

2. Anticancer Activity

The link between diet and cancer risk is well-established, with specific dietary components having either beneficial or detrimental effects on cancer development. As a result, chemoprevention, which involves the long-term pharmaceutical management of cancer risk, has gained attention in the field. Researchers have recently focused on natural products, particularly plant-derived compounds, investigating their potential as anticancer agents. Notably, approximately 70% of medications employed in cancer therapy are derived from natural products, underscoring the significance of plant-based compounds in cancer research[16,17].

Among numerous plant species examined for their potential anticancer attributes, *R. officinalis* has emerged as a highly promising candidate. Many research findings have demonstrated the potential of its extracts to halt cancer cell growth and initiate apoptosis, a vital process for maintaining tissue homeostasis. A study, by Allegra *et al.*,[10] demonstrated that the extract effectively blocked tumor development in mice by obstructing carcinogens from attaching to the DNA in the epidermis. Research has also underscored the apoptotic effects of the extract and its major compound, carnosic acid, in reducing the viability of colon cancer cells. These observations point to the plant as a promising agent in halting or delaying the advancement of colon cancer[18]. *In vitro* experiments using HCT116 and SW480 cancer cell lines revealed that the extract increased the expression of Nrf2 and sestrin-2, two critical factors in cellular defense against oxidative stress and inflammation. Moreover, *in vivo,* studies using colon cancer xenografted mice demonstrated a reduction in tumor size after treatment with the extract[10]. A recent study conducted by Pradeep *et al.*,[19] investigated the potential of *R. officinalis* in fighting cancer. The researchers specifically examined its effects on KB cell lines and observed that higher concentrations of the extract led to a reduction in the survival of these malignant cells. Furthermore, the study revealed that the extract influenced the apoptotic signalling pathway by reducing the expression levels of matrix metalloproteinase (MMP-9) and tumor-inducing metalloprotein mRNA. This was demonstrated through the use of RT-PCR analysis. The research community has been actively exploring the anticancer properties of both *R. officinalis* extracts and its essential oil. Ahamad *et al.*,[20] revealed in their study that its oil exhibited dose-dependent cytotoxicity against human breast adenocarcinoma cells, indicating its ability to target cancer cells selectively. Additionally, *in vitro*, experiments have shown that a raw extract from the fruit of the plant is quite effective at killing stomach cancer cells and a certain type of esophageal cancer cells. Interestingly, the stomach cancer cells were more vulnerable to this extract than the oesophageal cancer cells. When researchers looked closer, they found that the *R. officinalis* extract was stopping these cancer cells from progressing through a critical phase of their life cycle, the G2/M phase, which is essential for cell division and growth[21]. In a related study, a specific component found in *R. officinalis* called Sageone initiated apoptosis in SNU-1 human stomach cancer cells that usually do not respond well to cisplatin, a common chemotherapy drug. Unlike cisplatin, which tends to ramp up a protein associated with cancer cell survival called phosphorylated Akt, Sageone reduced this protein's levels. When Sageone was combined with a smaller, less harmful dose of cisplatin, it significantly boosted the death of these tough-to-treat cancer

cells. This combo led to an upregulation of certain proteins, specifically caspase-3 and caspase-9, which are hallmarks of cell death. The evidence suggests that Sageone might be a powerful new option for fighting cancer, especially in cases of stomach cancer[22]. The extract inhibits the Akt/mTOR/p70S6K signalling pathways, essential for the survival and growth of A549 human lung cancer cells[23]. Another study highlighted the potent anticancer properties of *R. officinalis* extracts, which significantly reduced cell viability in U937 and CaCo-2 cell lines, with respective IC_{50} values of 14.85 µg/mL and 14.95 µg/mL. The extracts prompted apoptosis and induced cell cycle arrest at the S phase in both cells[24]. Similarly, the methanolic leaf extract of *R. officinalis* demonstrated significant cytotoxicity towards A549 lung cancer cells[25]. Various compounds in *R. officinalis*, like ursolic acid, carnosic acid, betulinic acid and, rosmarinic acid, are credited with its anticancer properties[26]. Carnosic acid emerges as a major contributor to the reduction of breast cancer cell line survival among these compounds[27,28]. Hatami *et al.,*[29] demonstrated the cytotoxic effects of alginate nanoparticles with *R. officinalis* essential oil and its main component, α-pinene, on A-375 and MCF-7 cell lines. The study reported significant cytotoxicity with IC_{50} values indicating potent activity against MCF-7 cells. RT-PCR analysis revealed altered expression of apoptotic genes, with the Bax/Bcl-2 ratio suggesting the involvement of apoptotic pathways. Molecular docking studies have suggested that *R. officinalis* could also be effective against oral, ovarian, kidney, pancreatic, and prostate cancers[30].

The anticancer potential of *R. officinalis*, specifically due to compounds like carnosic acid, rosmarinic acid, and carnosol, has been highlighted in multiple studies. These compounds show anti-inflammatory, antioxidant, and pro-apoptotic activity, with carnosol diterpene being shown to induce ER stress and autophagy in cancer cells. Carnosol regulates key signalling pathways, such as p38 and ERK1/2, resulting in decreased cell division and increased apoptosis. It demonstrated toxic effects in MCF-7 and MDA-MB-231 breast cancer cell lines and enhanced the effectiveness of chemotherapeutic drugs tamoxifen. It triggers apoptosis through the TRAIL/p53 pathway and inhibits cell proliferation by targeting the androgen receptor and inducing ER stress[31]. Carnosic acid slows down the growth of HCC cell lines like Hep-G2, SK-HEP1, MHCC97-H, and Bel7402. It does this by triggering cell death through the routes connected to the mitochondrial pathways activating caspase-3, and PARP cleavage, and increasing the Bax/Bcl-2 ratio. CA also inhibits the Akt/mTOR pathway, leading to reduced tumor growth *in vivo*[32,33]. CA shows potent anticancer effects in CRC cell lines (HCT116, SW480, and HT-29) by inhibiting STAT3 activation and inducing ER stress. It causes cell cycle arrest and apoptosis through the Nrf2/Sestrin-2 pathway and enhances ROS accumulation, leading to cell death[18,34]. RA has shown significant anticancer effects against hepatocellular carcinoma cell lines, including Hep-G2 and SMMC-7721. RA triggers the process of apoptosis by enhancing the expression of proteins linked to apoptosis such as Bax and cleaved caspases-9 and -3, and simultaneously diminishing the Bcl-2 expression that prevents apoptosis. Additionally, it halts cell migration and invasion by suppressing metalloproteinases and modulating the PI3K/AKT/mTOR pathway[35,36]. RA inhibits the proliferation of CRC cell lines (CT26 and HCT116) by inducing cell cycle arrest at the G0/G1 phase and promoting apoptosis through intrinsic and extrinsic pathways. It activates the AMPK pathway and inhibits epithelial-mesenchymal transition, thereby reducing metastasis and invasion[37]. RA lowers the survival rate of MDA-MB-468 breast cancer cells, in accordance with dosage. It upregulates pro-apoptotic proteins such as HRK, TNF-α, and GADD45A, leading to apoptosis. RA also causes cell cycle arrest and downregulates the anti-apoptotic gene BIRC5, enhancing its anticancer effects[38]. In another study, rosmarinic acid exhibited significant anticancer effects by reducing cell viability, growth, invasion, and migration in pancreatic cancer cells, while promoting apoptosis. These effects were mediated through the up-regulation of miR-506, which targets and suppresses MMP2/16, key proteins in cancer progression[39]. RA inhibited the proliferation of Pancreatic Ductal Adenocarcinoma (PDAC) cell lines by inducing G0/G1 cell cycle arrest and impeding both metastasis and invasion. It modulates the Gli1 expression and its associated genes, leading to apoptosis through the intrinsic pathway[40]. The PI3K/Akt/mTOR pathway is often upregulated in various cancers. Carnosic acid reduced the expression of AKT1, mTOR, and survivin proteins in gastric cancer cells[41]. Although the existing data endorse the potential use of *R. officinalis* in chemotherapy (Figure 1, explaining the

anticancer mechanisms of *R. officinalis*)., more research is required to ascertain whether the anticancer effects can be primarily attributed to particular polyphenols or the combined impact of all components present in the extract. The promising anti-proliferative and anti-tumorigenic characteristics suggest potential applications in cancer therapies. Nevertheless, additional investigations are needed to elucidate their mechanisms and optimize their application fully.

3. Antioxidant Activity

The significance of plant-based antioxidants in the fields of nutrition and preventative healthcare is increasingly being recognized[42]. The *Lamiaceae* family has garnered particular interest among various plant families due to its high polyphenol content and a potential source of antioxidant molecules[43]. Using synthetic antioxidants in food production may have long-term health consequences, making natural antioxidants like *R. officinalis* an appealing alternative.

Rosmarinus officinalis, stands out as one of the most significant natural sources of antioxidants. Extensive literature supports *R. officinalis* well-established antioxidant activity, primarily attributed to the chemical compounds in its extracts and essential oils. Numerous research studies have documented the antioxidant characteristics of *R. officinalis* extracts and essential oils[44,45]. The EO of *R. officinalis* contains a rich concentration of natural antioxidants that can shield the body from oxidative stress, a phenomenon known to cause physiological disturbances in cells and lead to various diseases. Oxidative stress destroys vital biomolecules and cellular organelles[46]. The study by Ouknin *et al.,*[47] assessed the antioxidant potential of cultivated *R. officinalis* essential oil for possible use in the pharmaceutical and food industries. The essential oil showed strong antioxidant activity in various assays, with IC_{50} values of 337.23 µg/mL in the DPPH assay, 215.75 µg/mL in the β-carotene assay, and 265.45 µg/mL in the FRAP assay.

Research has explored the antioxidant potential *of R. officinalis* in different contexts. For instance, studies evaluated the antioxidant capacity of *R. officinalis* and *Hyssopus officinals* extracts by blending them with pork meat, and it was observed that the extracts mixed with cooked meat inhibited heme pigment degradation and lipid oxidation, thereby stabilizing the meat flavour and

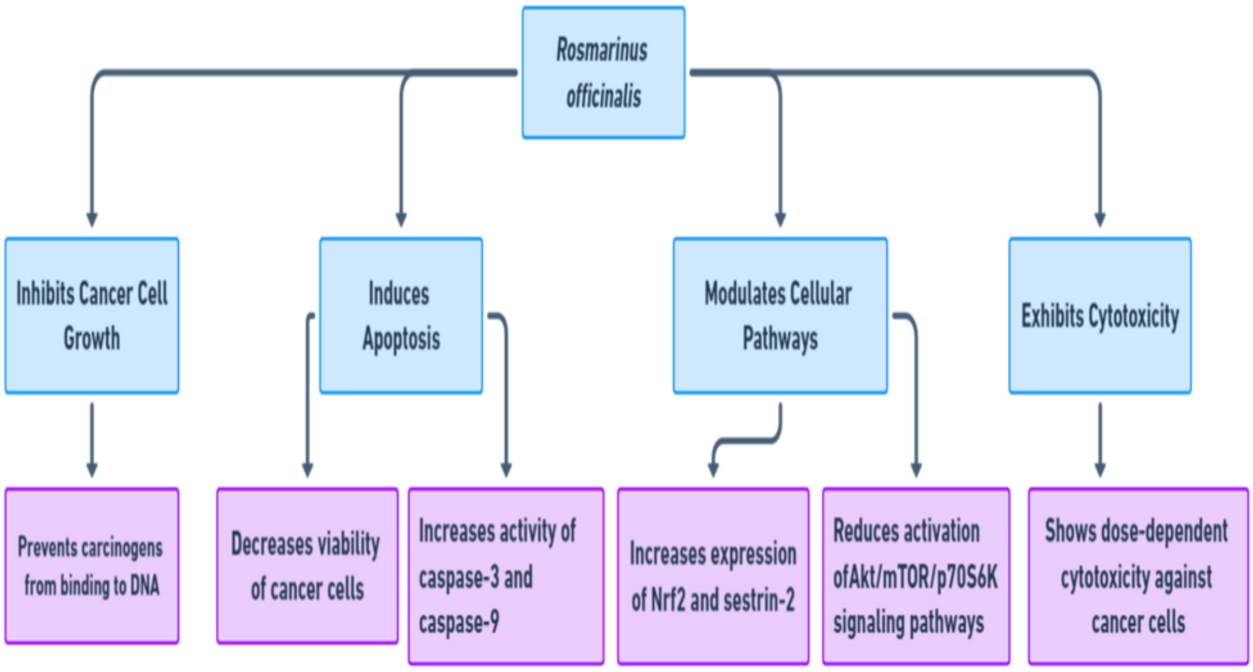


Figure 1. Diagram explaining the anticancer mechanisms of *R. officinalis*. It demonstrates its ability to inhibit cancer cell growth by preventing carcinogens from binding to DNA. Rosemary induces apoptosis by decreasing cancer cell viability and increasing the activity of caspase-3 and caspase-9. It also modulates cellular pathways by increasing the expression of Nrf2 and sestrin-2, while reducing activation of the Akt/mTOR/p70S6K signaling pathway.

prolonging its shelf life[48]. Similarly, *R. officinalis* extract significantly delayed lipid oxidation in vacuum-packed rainbow trout, prolonging the shelf life of the samples by up to four days compared to control samples without the extract[49]. Incorporating *R. officinalis* extract into animal diets has also improved lipid stability[50,51]. Moreover, its essential oils have demonstrated an inhibitory effect, protecting rat livers from oxidative damage induced by CCl_4[52]. *R. officinalis* essential oils have also been demonstrated to be efficient radical scavengers, preventing rancidity in industrial and household food items and extending their shelf life. Numerous studies have compared its antioxidant potential to synthetic antioxidants, with extracts showing greater efficacy than BHA (a synthetic antioxidant). Additionally, it has been employed as an antioxidant additive in oils, notably enhancing the shelf life of hazelnut oil by significantly reducing oxidation by-products during deep frying[53]. The extract effectively prevented ghee (clarified butter) from autooxidation, prolonging its shelf life and thermal stability without compromising its original physicochemical properties[54]. *R. officinalis* leaf extract displayed strong antioxidant activities, with notable results in assays such as DPPH (IC_{50} = 40.76 µg/mL) and FRAP (32.17 to 1.28 µm Fe (II)/g)[55]. These findings highlight its potential as an effective antioxidant for combating lipid oxidation and rancidity in the food industry. The essential oil of the plant has been tested using various assays, confirming its potent antioxidant activity[56]. Notably, essential oil obtained through Microwave Assisted Hydrodistillation exhibited enhanced ABTS and DPPH scavenging activities, with IC_{50} values of 0.66 mg/mL and 5.47 mg/mL, respectively, surpassing those of essential oils obtained through traditional hydrodistillation and method[57].

Another research found that PEF-RO's ability to neutralize DPPH radicals increased as its concentration did. The IC_{50} value of Petroleum ether fraction-RO was calculated to be 0.3606 mg/mL. In comparison, Vitamin C's value was much lower at 0.0212 mg/mL[58]. Compounds like carnosic acid and carnosol present in *R. officinalis* have shown strong peroxyl radical scavenging properties, surpassing artificial antioxidants like BHA, and BHT in their impact on membrane lipid peroxidation[59]. RA treatment mitigated oxidative damage in C6 glial cells by enhancing cell survival and minimizing lipid peroxidation. RA was found to inhibit the activation of COX-2 and iNOS proteins in cells exposed to H_2O_2[60]. This compound's strong antioxidant action helps neutralize harmful free radicals in hepatic stellate cells, leading to increased GSH levels and a reduction in MMP-2 activity, all driven by the NF-κB signalling mechanism. Similarly, RA reduces lipid peroxidation and ROS production, while increasing cellular GSH in HSC-T6 cells[61].

In summary, natural antioxidants derived from plants, particularly *R. officinalis*, have gained significant attention in nutritional and preventative medicine. *R. officinalis* extracts and essential oils are effective antioxidants, preventing oxidative stress and increasing food shelf life. Their efficacy has been observed in various contexts, including meat products, animal diets, and oils. Natural antioxidants like *R. officinalis* offer a promising alternative to synthetic antioxidants, ensuring long-term health benefits and stability in various applications.

4. Antimicrobial Activity

The increasing utilization of antibiotics across various domains, such as healthcare, farming, and animal husbandry, has resulted in the rise of multidrug-resistant bacteria, posing a major global health threat[62,63]. As a result, researchers are amplifying their endeavours to uncover innovative antimicrobial solutions. Interest in exploring plant-based sources has been increasing due to their capacity to produce antimicrobial compounds during regular growth, naturally developed, and in response to stress or pathogenic threats. This has prompted investigations into the efficacy of plant extracts, essential oils, and isolated phytochemicals as a promising strategy to counteract microbial proliferation[64,65].

The potent antibacterial capabilities of *R. officinalis* have drawn considerable research attention[46]. The strong antibacterial properties of the plant are due to various phytocompounds found in its extracts and essential oils[45]. Notably, Stojiljkovic *et al.,*[66] examined the antimicrobial effectiveness of its essential oil against various pathogenic bacteria. Their findings revealed significant activity against Gram-positive bacteria, with inhibition zones ranging from 18.0 to 24.2 mm and Minimum Inhibitory Concentrations (MIC)

between 0.20 and 0.48 mg/mL. In contrast, its efficacy against Gram-negative bacteria was lower, with inhibition zones of 12.8 to 17.5 mm and MIC values ranging between 1.16 and 1.72 mg/mL. The antimicrobial mechanisms include cell membrane disruption, cell wall degradation, and protein damage. *R. officinalis* essential oils have demonstrated robust activity against pathogens responsible for Urinary Tract Infections (UTIs)[67,68]. Specifically, Al Zuhairi *et al.,*[69] found that the essential oil of *R. officinalis*, enriched with 17.6% 1,8-cineole and 16.9% pinene, exhibited strong antibacterial activity against UTI-causing bacteria. Furthermore, Tsai *et al.,*[70] and Fu *et al.,*[71] conducted research that underscored the significant antibacterial effects of *R. officinalis* essential oil against bacteria responsible for acne, suggesting its potential as an alternative to traditional antibiotics. Additionally, investigators have explored the combined effects of *R. officinalis* with conventional antibiotics. Jarrar *et al.,*[72] assessed the antibacterial activity of its extract both independently and in conjunction with cefuroxime against MRSA. The combination demonstrated a synergistic effect, lowering the MIC of extract against MRSA. Similarly, Jiang *et al.,*[73] observed that the essential oil of *R. officinalis* exhibited more potent activity against several bacteria, like *Escherichia coli, Staphylococcus epidermidis, Proteus vulgaris, Bacillus subtilis,* and *Pseudomonas aeruginosa,* compared to specific compounds like 1,8-cineole and α-pinene. Moreover, studies by Rozman and Jersek showcased the robust antibacterial properties of *R. officinalis* extracts against various species of Listeria[74]. The inhibitory effects of *R. officinalis* extracts and essential oils on pathogenic microbes are due to various compounds, like epirosmanol, carnosic acid, rosmaridiphenol, carnosol, isorosmanol, rosmarinic acid and rosmanol[46]. These constituents affect the microbial cell membrane, leading to genetic and metabolic alterations that impede their growth and survival. In a study by Qabaha[73], the microbial potential of ethanolic extracts sourced from five different plants was assessed using the good diffusion technique. Among the tested extracts, only the *R. officinalis* extract demonstrated activity against the Gram-negative bacterium *P. aeruginosa*, a pathogenic microorganism known for its resistance to conventional treatment approaches. The investigation observed a significant inhibition of 16 mm with 25 mg of the ethanolic *R. officinalis* extract per well[75]. In contrast, conventional antibiotics such as penicillin, gentamycin, and ciprofloxacin were ineffective against *P. aeruginosa*[76]. Additionally, hydro-alcoholic extracts from *R. officinalis* leaves have shown effectiveness against dermatophytes, inhibiting fungal growth and causing morphological changes in hyphae[77]. *R. officinalis* methanolic extracts, especially from plants grown under saline conditions, exhibit significant antimicrobial activities against *Micrococcus luteus*, *S. aureus, Clostridium perfringens* and *Candida albicans*. The increased antimicrobial activity is associated with higher essential oil content and changes in chemical composition, particularly the increased levels of camphor, endo-borneol, and linalool[78]. The methanolic extract of the plant showed strong antimicrobial activity against different microbial strains including *E. coli, Klebsiella pneumoniae* and *Enterobacter aerogenes*[79]. Studies have demonstrated the antifungal effects of *R. officinalis* essential oil on various Candida species, with research showing that an 8% concentration effectively suppressed their growth. Similarly, another study assessed the impact of a hydroalcoholic extract from the plant on the dermatophytes *Microsporum gypseum* and *Trichophyton rubrum*. The results showed that a 10% concentration of the extract caused an 86% reduction in fungal growth[80]. The diterpenes carnosic acid and carnosol, present in the leaves of *R. officinalis,* have been shown to specifically inhibit the expression of *S. aureus*, thereby disrupting its cell-cell communication system and reducing its pathogenicity[81]. Adibian *et al.,*[82] synthesized selenium nanoparticles (Se-NPs) using aqueous extracts of *R. officinalis*, which showed substantial antimicrobial effects against various pathogens, including *S. aureus*, *S. mutans*, *E. coli*, and *P. aeruginosa*. The MIC for these pathogens ranged from 16 to 128 µg/mL. Another study highlighted the effectiveness of *R. officinalis* in inhibiting the growth of significant meat-borne pathogens, including *E. coli*, *Salmonella* spp., and *Listeria monocytogenes*. These pathogens are of particular concern in the meat industry because of their ability to cause foodborne illnesses[83].

In conclusion, using plant-derived antimicrobial agents, particularly from *R. officinalis*, offers a promising avenue to combat the challenge of antimicrobial resistance. Extensive research on *R. officinalis* has

demonstrated its potent antibacterial activity against various pathogens, including those responsible for urinary tract infections and acne. Furthermore, combining *R. officinalis* with conventional antibiotics has shown synergistic effects, enhancing its efficacy. The bioactive compounds in *R. officinalis* extracts and essential oils play a crucial role in inhibiting the growth of pathogenic microbes. Continued exploration of plant-based antimicrobials, such as *R. officinalis*, holds significant potential for developing alternative strategies to address the global issue of antimicrobial resistance. As the search for effective antimicrobial agents continues, the rich reservoir of natural compounds in plants offers a promising solution to combatting antimicrobial resistance and ensuring a healthier future for humanity.

5. Antidiabetic and Antihyperlipidemic Activities

Diabetes mellitus is a metabolic disorder that leads to elevated blood sugar levels. Currently, more than 537 million adults worldwide are living with diabetes. By the year 2045, this number is projected to rise to 700 million. Diabetes management typically involves changes in lifestyle, drug treatments, and sometimes insulin therapy. However, these methods frequently cause unwanted side effects, prompting growing interest in medicinal plants as potential alternative or complementary treatments for diabetes[84]. Researchers have recently turned their attention to natural compounds as potential candidates for diabetes management. Different studies have explored the potential antidiabetic effects of *R. officinalis*, primarily focusing on its ability to regulate body weight, fat metabolism, glucose homeostasis, and lipid levels. In a study by Koga *et al.,*[85] on STZ-induced diabetic mice, a 50% ethanolic extract from *R. officinalis* was evaluated. The extract showed potential in controlling glucose uptake from the intestines by inhibiting the activity of α-glycosidase. Moreover, when rabbits with alloxan-induced diabetes were given *R. officinalis* ethanolic extract, there was a noticeable drop in their blood sugar levels and a rise in insulin levels. It's also worth noting that human studies have backed up the anti-diabetic abilities of *R. officinalis*[86]. Labban *et al.,*[87] administered *R. officinalis* leaf powder to male and female adults for four weeks Daily doses of 5 and 10 grams of leaf powder significantly lowered blood glucose levels, with the higher dose demonstrating a stronger effect. Total cholesterol and triglyceride levels were also reduced in all groups, indicating a potential role of *R. officinalis* in improving lipid profiles. Studies on cell lines have shed light on the underlying mechanisms of *R. officinalis 's* antidiabetic effects. Lipina and Hundal[88] found that glucose uptake was enhanced in L6 myotubes treated with *R. officinalis* extract. Similarly, Naimi *et al.*,[89] found that carnosic acid improved glucose absorption in a way dependent on both time and dosage, even at low concentrations. Carnosic acid effectively reduces blood sugar levels during fasting. It also enhanced glucose tolerance and insulin sensitivity in experiments conducted on db/db mice. This improvement was attributed to a reduction in ROS accumulation. Additionally, carnosic acid was shown to ameliorate kidney damage, specifically by improving conditions of glomerular sclerosis and mesangial expansion. This improvement was linked to an increase in urine creatinine and a decrease in water retention, urine output, albumin in the urine, and blood glucose levels, which was mediated through the Nrf2/NF-κB signalling pathway, suggesting a protective effect against diabetic nephropathy[90]. Rosmarinic acid, another compound studied, was found to have antidiabetic properties by restoring pancreatic β-cell function. This restoration occurred by activating Nrf2 and HO-1 while halting the NF-κB signalling pathway in rats with a high-fat diet and STZ-induced type 2 diabetes. The activation of the Nrf2-Keap1 pathway resulted in higher HO-1 expression and increased ARE-driven luciferase activity[91]. This mechanism is advantageous for ameliorating diabetic microangiopathy in human microvascular endothelial cells. and reduce inflammatory markers (IL-6, and TNF-α) and oxidative stress markers including MDA, TC, TG, and LDL-C. Conversely, it elevated the levels of antioxidants, including glutathione-s-transferase, superoxide dismutase, catalase, and HDL-C, in streptozotocin-induced diabetic rats. These findings suggest that carnosol and rosmarinic acid improve diabetes symptoms and complications by mitigating inflammation and oxidative damage[92,93]. ROP (Rosemary Extract Powder) significantly reduced blood glucose levels in animals with streptozotocin-induced diabetes. In addition, the administration of

ROP as a dietary supplement led to notable reductions in ALT, AST, bilirubin, LDL levels total triglyceride, and total cholesterol, while significantly increasing HDL compared to diabetic control[94].

In a study by Harach *et al.*,[95], mice on a high-fat diet were treated with *R. officinalis* extract. The results demonstrated a significant decrease in body weight and fat accumulation, along with an increase in lipid excretion through the faeces. The researchers linked these effects to the inhibition of pancreatic lipase enzymes. Furthermore, the *R. officinalis* extract decreased triglyceride levels in the liver. Carnosic acid, found in *R. officinalis*, was identified as a key player in preventing hepatocyte lipid accumulation. Wang *et al.*,[96] found that CA reduced PPARγ levels and activated the EGFR/MAPK signalling pathway, thereby preventing lipid buildup. Although findings are promising (Figure 2, explains how *R. officinalis* influences various antidiabetic activities, Figure 3, explains how *R. officinalis* influences various antihyperlipidemic), further analysis is necessary to uncover the mechanisms and pathways through which *R. officinalis* exerts its antidiabetic effects. Additionally, it is essential to evaluate the preventive effects of its main compounds on obesity, diabetes, and associated complications. Furthermore, human studies are needed to validate the positive effects of *R. officinalis* on body weight, body fat, and glucose regulation.

6. Neuroprotective and Memory-enhancing Effects of *R. officinalis*

Depression and anxiety are common mental health challenges that impact countless individuals worldwide. Traditional approaches to managing these conditions often rely on drugs, yet there is rising interest in identifying natural solutions that could offer benefits for mental well-being. *R. officinalis*, known for its culinary and therapeutic applications, has been examined in various studies for its potential to enhance mood and cognitive function[97,98]. Research has shown that *R. officinalis* essential oils and extracts can improve cognitive dysfunction and mitigate neurodegenerative processes. Specifically, compounds such as carnosic acid β-pinene, and rosmarinic acid, have demonstrated efficacy in improving cognitive functions and safeguarding neuronal cells against oxidative damage and beta-amyloid toxicity, common pathways implicated in Alzheimer's Disease (AD). These effects were observed in various preclinical models, suggesting that its bioactive components can cross the blood-brain barrier, offering protective

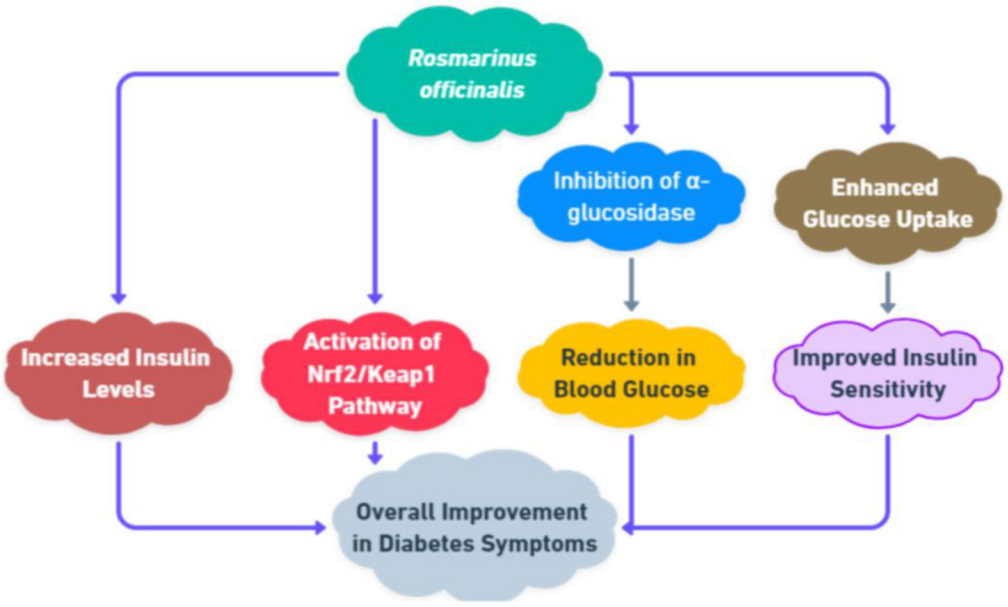


Figure 2. Diagram explaining the antidiabetic mechanisms of *R. officinalis*. It illustrates its role in enhancing glucose uptake, increasing insulin levels, and reducing blood glucose. Key mechanisms include the inhibition of α-glucosidase activity and activation of the Nrf2/Keap1 pathway.



Figure 3. Diagram explaining the antihyperlipidemic mechanisms of *R. officinalis*. It depicts its ability to lower cholesterol, fat mass, LDL-C, and triglycerides while increasing HDL-C. Key processes include pancreatic lipase inhibition, enhanced lipid excretion, reduced liver triglycerides, prevention of hepatocyte lipid accumulation, and activation of the EGFR/MAPK pathway, illustrating its therapeutic potential in managing hyperlipidemia.

effects against neurotoxicity[99-101]. 1,8-Cineole, a lipid-soluble compound found in *R. officinalis* essential oil, efficiently crosses the Blood-Brain Barrier (BBB). Once in the brain, it exerts its effects by interacting with neuronal receptor sites and influencing enzyme activity, contributing to its neuroprotective properties[102]. Similarly, carnosic acid, another key compound in *R. officinalis*, crosses the BBB primarily due to its lipophilic nature. Upon encountering regions of redox stress, it undergoes oxidation to become an active electrophilic form. This active form interacts with Keap1, a regulatory protein, releasing Nrf2 — a critical transcription factor. Nrf2 then migrates to the nucleus and triggers the expression of antioxidant genes. This dual action allows carnosic acid not only to penetrate the BBB but also to activate endogenous antioxidant pathways, offering significant protection within the nervous system[103,104].

Rosmarinus officinalis's remarkable antioxidant benefits stem primarily from two key compounds: rosmarinic acid and carnosic acid. These bioactive substances combat oxidative stress by neutralizing free radicals and enhancing the body's natural antioxidant defences. Carnosic acid, in particular, plays a vital role in protecting neuronal cells. It preserves mitochondrial membrane potential and reduces the production of ROS, crucial factors in cellular health. Furthermore, studies have shown that carnosic acid mitigates the loss of cell viability caused by amyloid-beta (Aβ) in neuroblastoma cells, highlighting its potential in preventing the progression of Alzheimer's disease[105]. Inflammation has a significant role in the progression of

neurodegenerative diseases. *R. officinalis* extracts have shown anti-inflammatory properties by modulating the activity of inflammatory mediators. The bioactive compounds in *R. officinalis* reduce neuroinflammation by inhibiting the synthesis of pro-inflammatory enzymes and cytokines. Studies have shown that carnosol, a component of *R. officinalis*, can inhibit pathways like the Raf-MEK-ERK1/2 pathway, which are involved in the inflammatory response and cell death in dopaminergic neurons, a characteristic feature of Parkinson's Disease[106]. *R. officinalis* has been found to inhibit acetylcholinesterase and butyrylcholinesterase, enzymes responsible for the acetylcholine breakdown, a neurotransmitter important for learning and memory[107]. By inhibiting these enzymes, it helps increase the levels of acetylcholine in the brain, thereby improving cognitive functions. Ozarowski *et al.,*[108] reported that *R. officinalis* leaf extract improved memory impairment in rats by modulating AChE and BChE activities, crucial for neurotransmitter dynamics associated with memory. This plant affects various neurotransmitter systems, including dopaminergic and oxytocinergic systems, which play a role in mood regulation, memory, and cognition. For instance, compounds in it have been shown to enhance the dopaminergic system by upregulating the expression of dopamine synthesizing. tyrosine hydroxylase. This is particularly relevant in the context of Parkinson's Disease, where dopaminergic neurons are progressively lost[106,109].

In a study by Ferlemi *et al.,*[110], the anxiolytic and antidepressant impact of *R. officinalis* tea on adult male mice was evaluated through a series of behavioural tests over four weeks. The outcomes highlighted a positive effect on anxiety and depressive behaviours in mice without impairing their cognitive capabilities, suggesting the plant is a promising natural treatment for mood disorders. Machado *et al.,*[111] delved into the antidepressant potential of *R. officinalis* extract in mice after an olfactory bulbectomy, a depression model. The study found that the extract displayed antidepressant properties and counteracted the alterations in Acetylcholinesterase (ACHE) activity caused by the surgery. Since AChE plays a role in breaking down acetylcholine a neurotransmitter linked to mood—the results propose a possible way through which *R. officinalis* extract could influence neurotransmitter systems implicated in depression. Pengelly *et al.,*[112] conducted a placebo-controlled, double-blind study with older adults to assess the impact of *R. officinalis* powder on cognitive performance, utilizing a computerized test system. The study showed that *R. officinalis* notably improved memory speed over the placebo, even at dietary doses, pointing to its cognitive-boosting potential relevant for depressive cognitive symptoms. Habtemariam *et al.,*[113] explored the neuroprotective effects of carnosic acid from *R. officinalis* against cyanide-induced brain damage using rodent and human-derived neurons *in vitro* and a mouse model *in vivo*. The results showed carnosic acid protected against cyanide-induced neuronal damage, highlighting its neuroprotective qualities that could be beneficial in preventing or reducing neuronal damage in depression.

Nonetheless, despite these promising outcomes, further studies are needed to fully understand *R. officinalis's* action mechanisms and its clinical efficacy in treating depression and anxiety. More extensive and longer-term human clinical trials are essential to confirm its antidepressant benefits. It is also crucial to investigate any possible side effects and interactions with conventional medications to ensure *R. officinalis* can be safely used as a complementary or alternative option for mood disorder treatments.

7. Conclusion

In conclusion, the extensive research conducted on *R. officinalis* has provided scientific validation for many of its traditional uses. The findings discussed in this article highlight its potential as a valuable asset in medicine, offering possibilities for treating and preventing various diseases. One area where *R. officinalis* shows promise is in the realm of cancer. Numerous studies have supported the significant anticancer properties of *R. officinalis* extracts. However, it is crucial to emphasize that more comprehensive animal studies are needed before moving forward with human trials. These animal studies can help determine optimal doses, the most effective route of administration, plasma levels of bioactive ingredients from *R. officinalis*, the specific signalling molecules and pathways influenced by the plant, and any potential toxic effects associated with long-term use. In addition to anticancer potential,

R. officinalis exhibits beneficial effects in combating infectious diseases, oxidative damage, diabetes, and hyperlipidemia. However, more investigation is essential to confirm the safety and therapeutic potential for use in these areas. Additionally, future research should focus on conducting clinical trials to evaluate the efficacy and safety of *R. officinalis* in humans, as well as investigating the bioavailability and pharmacokinetics of its key active compounds. These studies will help bridge the gap between laboratory findings and therapeutic applications in real-world scenarios.

7. Author Contribution

AM T, AN, MAS conceptualized and designed the study, conducted the literature review, and contributed significantly to the drafting and revision of the manuscript. AM T led the data analysis and interpretation of results, while Anima Nanda provided critical insights into the pharmacological aspects. Mohmmad Ashaq Sofi played a pivotal role in manuscript preparation and coordination of the research team. MAS and BKN contributed to data collection and provided additional resources and references. All authors reviewed and approved the final version of the manuscript.

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