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Anticancer and Other Therapeutic Effects of Rosemary

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Abstract**—** *Cancer cells have accelerated growth rates and resistance to apoptosis. Cancer cells develop the capacity to resist homeostasis, proliferate uncontrolled, and avoid programmed cell death/apoptosis due to mutations in important signalling molecules that control the pathways involved in cell survival and proliferation. Recently, the European Union (EU) and the Food and Drug Administration in the United States both approved rosemary extracts that were standardised to diterpenes (such as carnosic acid and carnosol) (FDA). The possibility of exposure to rosemary's diterpenes has increased as a result of its use in our food system and dietary choices (such as the Mediterranean Diet). According to reports, diet, especially consumption of vegetables and specific plant substances, plays a significant influence in lowering the chance of developing cancer. The ubiquitous household plant rosemary, which is grown all over the world, has recently attracted a significant amount of scholarly interest. Additionally, colon and prostate cancer xenograft in mice were suppressed by the rosemary extract and diterpenes. Compared to diterpenes, rosemary extract is more cytotoxic since it contains polyphenols like triterpenes and flavonoids. As a natural food preservative and therapeutic agent in the treatment of numerous diseases, Rosmarinus officinalis shows great promise. Several compounds known to be potent antioxidants are present in both the essential oil and extract of rosemary. The antioxidant activity of rosemary is essential to many of its biological activities. simply given that oxidative stress is a serious consequence of both diabetes and cancer, this is particularly true of rosemary's anti-diabetic and anti-cancer processes.*

Keywords**—** *Rosmanol, Carnosol, carnosic acid, rosemary extract, Diterpene, Types of cancers,Other uses*.

I. INTRODUCTION

Because colon and prostate cancer cells are the most sensitive, rosemary extract, carnosic acid, carnosol, and rosmanol's anticancer effects are concentrated on these cancerous cells. Their cytotoxic effects include the inhibition of cancer cell development, several molecular targets, and various signalling pathways. Growth inhibition includes apoptosis, antiproliferation, and cell migration inhibition. This overview discusses the botany, chemistry, and anticancer properties of rosemary extract and its main diterpenes, carnosic acid, carnosol, and rosmanol. Cancer cells' increased proliferative capacity and decreased apoptotic capacity are arguably their most fundamental characteristics.The creation and release of growth factors, which control cell growth and proliferation, is strictly regulated by normal cells, ensuring cellular homeostasis and maintaining the structure of normal tissue. These signals are dysregulated in cancer cells, which affects the body's equilibrium. The cell has been damaged. Numerous factors can promote the growth of cancer cells. Growth factors may be produced by cancer cells, and these cells can react by expressing the appropriate receptors. It is also possible for cancer cells to express higher levels of receptor proteins, which makes them more sensitive to growth factors. The same effect can also be achieved by altering the receptor molecules to enable the activation of downstream signalling cascades without growth factor binding [1]. Alternately, normal neighbouring cells may receive signals from cancer cells, changing or mutating the signalling pathways. These modifications cause the growth factors to be released, which are then fed back to the cancer cells to promote their proliferation [2,3]. Plasma membrane proteins with intrinsic tyrosine kinase activity are known as growth factor receptors (GFR), including epidermal GFR (EGFR). Growth factor binding increases the receptor's tyrosine kinase activity, which results in the autophosphorylation of the receptor. For intracellular proteins carrying the receptor's phosphorylated tyrosine residues to bind, Src-homology 2 (SH2) domains stimulate intracellular signalling cascades like the PI3K-Akt and Ras-mitogen activated protein kinase (Ras-MAPK) cascades, resulting in increased proliferation and decreased apoptosis/improved survival. The three stages of cancer development are initiation, promotion, and progression. An alteration to a cell's genetic make-up during initiation prepares the cell to develop into cancer. Multiple variables allow a single mutant cell to survive (fight apoptosis) and proliferate throughout the stage of promotion, encouraging a tumour to grow. Finally, the disease condition advances as the malignant cell multiplies and grows into a tumour. As healthy, normal cells move to a neoplastic state, they gain a number of distinguishing qualities that allow them to develop into cancerous cells. Hanahan and Weinberg identified 6 hallmarks of cancer, including maintaining proliferative signals, dodging growth inhibitors, enabling replicative immortality, resisting cell death, promoting angiogenesis, and triggering invasion and metastasis. These characteristics will start to show up more frequently as tumours develop and become more aggressive. Depending on the stage of carcinogenesis they target, current anticancer treatments can be categorised as either chemopreventive or chemotherapeutic. Cells in culture or animal models can be exposed to an anticancer agent before

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being exposed to a carcinogen in order to investigate the chemopreventive potential of anticancer drugs. This shows how an anticancer agent affects the cancer's beginning and promotion stages. As an alternative, cells in culture or animal models may be subjected to a carcinogen to induce a neoplastic state before being treated with an anticancer agent, and this gives proof of the anticancer agent's effectiveness. on the development of cancer. Natural plant materials have been screened to find numerous medicinal compounds. Some of these medications, such the chemotherapeutics etoposide, separated from the Queen Anne's lace and mandrake plants, and paclitaxel and docetaxel, isolated from the Nyssaceae tree's wood and bark, are being used successfully in the treatment of cancer [4].

Diterpenes are C20 compounds that can be linear, bicyclic, tricyclic, tetracyclic, pentacyclic, or macrocyclic depending on the structure of their core skeleton (5). Because of their intriguing pharmacological and biological properties, they have attracted increased research interest. The tricyclic diterpenoids known as abietanes, which are found in rosemary, have three fused six-membered rings with alkyl functional groups at carbons 4, 10, and 13. (6). About 3000 of the 13,000 diterpenes found in plants are from the Lamiaceae family, also known as the mint family, which includes popular culinary and fragrant herbs like rosemary, sage, and thyme (7). The Lamiaceae is a large family. consists of 7852 species and 250 genera of flowering plants (8). Because flowers have petals that merge into top and bottom lips, the original family name was Labiatae. (9). The family name currently used by the majority of botanists is Lamiaceae. Worldwide, the family's species are used for a variety of therapeutic, culinary, and decorative purposes, and numerous biologically active essential oils have been discovered (10). In 127 nations around the world, cancer and cardiovascular disease are the main causes of early mortality (11).

II. Anti Cancer Activity

The anticancer properties of Rosmarinus officinalis have been the subject of numerous studies. Significant anti-proliferative effects of rosemary against a number of human cancer cell lines have been observed. Major plant extract constituents like carnosic acid, carnosol, and rosemarinic acid have been demonstrated to trigger apoptosis in these cancer cells, perhaps by nitric oxide production. According to several studies, carnosic acid is the most effective apoptosis promoter[12,13–14]. Also intriguing is the antitumorigenic effect of rosemary extract. By blocking carcinogens from binding to epidermal DNA, the extract was reported to significantly suppress the development of skin tumours in mice in one research [15]. The antioxidant activity of the extract is what gives rise to this anti-carcinogenic effect[16]. [These antiproliferative and antitumorigenic properties of R. officinalis call for further study since they may be applied in future cancer treatments.

1-Rosemary and colon cancer-

The cytotoxic effects of rosemary extracts on HGUE-C-1, SW480, and HT-29 colon cancer cells were significantly stronger at 48 hours than at 24 hours (17). On HT-29 cells, the extract was least effective, and prolonged treatments resulted in lower IC50 values. Six methanol rosemary extracts were tested for cytotoxicity using five different cancer cell lines (18). Extract I-SC had the highest activity against DU-145 colon cancer cells, with an IC50 value of 8.8 g/mL, due to the high concentration of carnosic acid (50 mg/g extract). The IC50 values for an enhanced rosemary extract against HT-29 and HCT116 colon cancer cells were 11-12 and 22-32 g/mL, respectively (19). The rosemary extract was improved and now contained 264 and 34 mg/g, respectively. Carnosic acid and carnosol extract are two different things. Carnosic acid had IC50 values of 27, 28, and 29 M in HCT116 cells after 24, 48, and 72 hours of treatment, respectively (20). Carnosol supplementation reduced the number of intestinal tumours while inhibiting the start, promotion, and progression stages of colon cancer cells in an animal study (21,22). According to a study, rosmanol strongly promoted apoptosis in COLO 205 colon cancer cells, with a 51% apoptotic ratio and an IC50 value of 42 M. (23) The anticancer effects and mechanisms of rosemary extracts, carnosic acid, carnosol, and rosmanol on colon cancer cells. DLD- and SW620 growth inhibition Because rosemary extract significantly reduced the number of colon cancer cells when compared to carnosic acid or carnosic acid alone or in combination, it is possible that substances other than carnosol and carnosic acid found in rosemary extract also contributed to its anticancer effects (24). According to proteomic profiling, carnosic acid and carnosol in rosemary extract both induced diverse Nrf2-mediated responses in HT-29 colon cancer cells (25). Similarly, carnosic acid and other polyphenols in rosemary extract reduced the viability of HT-29 and SW480 colon cancer cells, but not as effectively as the extract itself. Among the other polyphenols, rosmarinic acid is a plausible candidate for suppressing cell proliferation. HT-29(26). Rosmarinic acid is cytotoxic to colon cancer cells HCT15, CO115 (27,28), and Ls174-T (29). Other cytotoxic polyphenols in rosemary extract include triterpenes such as betulinic acid and ursolic acid. Betulinic acid's ability to cause cancer cell death by activating the mitochondrial apoptosis pathway is linked to its anticancer properties (30). Ursolic acid induces apoptosis in breast and colon cancer cells while inhibiting proliferation and angiogenesis (31).

2-Pancreatic Cancer-

Additionally, pancreatic cancer has been shown to be a pathology in which rosemary's anti-cancer effects have been established. The seventh most frequent cause of cancer-related death is this kind of tumour. Unlike other cancers, pancreatic cancer is becoming more common, yet there has been no improvement in raising the survival rate (32). Gonzalez-Vallinas et al. investigated the effects of supercritical REs on colon and pancreatic cancer cells. Data on a cell The cancer cells that are most responsive to RE are PANC-1 (pancreas), MIA-PaCa-2 (pancreas), SW620 (colon), and DLD-1, according to viability (colon). In fact, colon cancer cells respond more than pancreatic cancer cells to the extracts' antiproliferative properties. In terms of probable mechanisms,

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the anticancer effects of rosemary are connected with an increase in the metabolic-related gene GCNT3 and a decrease in its potential epigenetic modulator miR-15b. Moreover, following in vivo rosemary administration, a plasmatic miR-15b reduction was found (33).

3- Kidney Cancer-

Derivatives of rosemary seem to be a good target for urinary tract tumours. ROS-induced endoplasmic reticular stress caused by CA enhanced programmed cell death in Caki, kidney carcinoma cells. Additionally, CA increased the levels of apoptotic markers like ATF4, caspase3, and CHOP (34) and increased TRAIL-mediated apoptosis in Caki cells as well as other renal cell lines (AHCN and A498) via a change in endoplasmic reticular stress-related proteins like Bcl-2, CHOP, c-FLIP, DR5, Bim, PUMA, and CHOP (35) RE also has a cytotoxic effect on the cells that make up urinary bladder cancer 5637.

4- Breast Cancer-

Several studies have shown that REs and their derivatives are beneficial in the prevention and treatment of breast cancer. RE may reduce the survival of breast cancer cell lines, with CA proving to be the most effective component [36]. CS was discovered to be an antagonist of this receptor rather than an agonist, and it was proposed that it performs its antioxidant function via the oestrogen receptor (ER) signalling pathway [37]. The effects of CS on cell proliferation and its unique regulatory mechanisms in ER-positive breast cancer T47D cells have been studied [39]. Other types of cancer and rosemary Rosemary extracts are cytotoxic to cells with bladder, breast, cervical, leukaemia, liver, lung, ovarian, and pancreatic cancer (40). Carnosic acid is cytotoxic to cancer cells in the brain, breast, kidney, leukaemia, liver, lung, neural, oral, ovarian, pancreatic, renal, and skin (41). Carnosol is cytotoxic to breast, liver, ovarian, and skin cancer cells (42,43). Recent research has shown that carnosic acid has in vitro anticancer effects on skin and breast cancers, including leukaemia, as well as carnosol on skin cancer and rosemary extracts on liver, lung, and breast cancer, including leukaemia. Furthermore, research on the effects of rosemary extracts on breast, skin, and liver cancer has been conducted. Carnosol is used to treat oral cancer, whereas carnosic acid is used to treat skin and breast cancer (44). This review leads to the following anticancer activity ranking: rosemary extracts > carnosic acid > carnosol

Some other pharmacological actions

Antidiabetic Activity-

The prevalence of diabetes mellitus is rising globally. The number of diabetics worldwide is predicted to reach 300 million by 2025, with annual treatment expenditures rising to $1 trillion USD. High levels of oxidative stress frequently contribute to the development of diabetes; pancreatic -cells are particularly susceptible to reactive oxygen species, which results in decreased insulin release and increased blood glucose levels. This knowledge has led to an emphasis on natural antioxidants in emerging diabetic treatments, especially those found in plants. It is hardly unexpected that Rosmarinus officinalis has been identified by numerous research. as a potential anti-diabetic substance. The antioxidant capabilities of rosemary carry out a number of hypoglycemic and anti-diabetic actions. In one study, rosemary extract reduced blood sugar levels in rabbits with diabetes, hyperglycemia, and normal blood sugar. The extract enhanced insulin secretion by promoting lipid peroxidation inhibition and antioxidant enzyme activation [45]. Another significant consequence of diabetes, delayed wound healing, has been reported to be improved by rosemary [46]. The body's increased antioxidant status following rosemary supplementation is what causes these anti-diabetic effects[47].

Antidepressant Activity-

Many of the studies examined for this project focused on the potential antidepressant properties of Rosmarinus officinalis. The Tail Suspension Test (TST) and Forced Swimming Test are the two procedures most frequently employed in these experiments to simulate the effects of antidepressants on mice (FST). In both the TST and the FST, the treatment of rosemary consistently decreased the mice's immobility period, indicating an effect akin to that of an antidepressant [48,49]. When it was discovered that Rosemary reduced exploratory and anhedonic-like behaviour in bulbectomized rats, its antidepressant potential was further strengthened [50]

Anti-Inflammatory Activity-

In several of the studies reviewed, Rosmarinus officinalis demonstrated potent anti-inflammatory mechanisms. In vivo, rosemary essential oil and extract significantly inhibited leukocyte migration [51]. This reduced the number of leukocytes (White Blood Cells) at the inflammatory site, resulting in an anti-inflammatory response [52,53]. "However, we are likely still a long way from being able to use rosemary and its derivatives in clinical practise, and a significant number of issues remain unresolved."

Benefits of Rosemary-

Rosemary has several health benefits. It is famous for its essential oil. Because of the following properties, rosemary has a wide range of medical applications.

It may possess the following properties: anti-inflammatory, antioxidant, neuroprotective, antidepressant, antimicrobial, antidiabetic, anti-cancer, and anti-obesity properties. It may also have the following potential properties: anti-inflammatory, antioxidant, neuroprotective, anticancer, and anti-obesity properties.

Side effects or Rosemary-

1) Large doses of rosemary may cause kidney damage in addition to stomach and intestinal distress.
2) Although the plant has been linked to allergic contact dermatitis, rosemary is not typically regarded as a human skin sensitizer. Monoterpene ketones, one of rosemary's ingredients, have been known to induce seizures when taken in high concentrations. Additionally an abortion, Rosemary.
3) Toxic effects from ingesting significant amounts of the oil are possible.
4) promotes menstrual blood loss.
5) might lead to miscarriage.

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6) Death and coma.

III. CONCLUSIONS

This overview summarised the chemistry and anticancer effects of rosemary extract and its diterpenes. Studies on phytochemistry are fruitful because the genus Rosmarinus and the species R. officinalis continue to produce substances that are novel to science. Rosemary contains over 30 chemicals that have anticancer properties. Because current therapy is frequently ineffective due to side effects, novel medication treatments are required for neoplastic disorders. It has been established that various natural items are effective in the prevention and treatment of various tumour types. According to studies, rosemary inhibits carcinogen activation, increases antioxidant enzyme activity, decreases tumor-stimulating inflammation, slows cell growth, promotes programmed cell death, and inhibits tumour angiogenesis and invasion [54].

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