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ANTICANCER POTENTIAL OF ROSMARINIC ACID ON DIFFERENT CANCERS: A REVIEW ON ITS PLAUSIBLE THERAPEUTIC POTENTIAL

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Abstract:

Rosmarinic acid is a polyphenolic compound with numerous pharmacological actions anti-inflammatory, immunomodulatory, and neuroprotective, as well as having antioxidant and anticancer activities. This article reviews the anticancer effects and mechanisms of Rosmarinic acid action in cell lines, animal model systems as well as human trials. The article discusses the cytotoxic and antiproliferative effects of the said phytochemical in dose and duration dependent manner. Amazingly, Rosmarinic acid induced cell cycle arrest and induction of apoptosis by altered the expression of many apoptotic genes differently has been extensively study throughout the world. In various cancer cell lines, Rosmarinic acid has been found to arrest cells in the G_0/G_1 phase. The article also aimed to review animal model studies wherein animals with induced cancers treated with Rosmarinic acid showed significant lower tumour cell viability, proliferation and invasive abilities as compared with normal cells. In conclusion the review of literature showed that Rosmarinic acid exerted apparent inhibitory effect on cancer cells in cell line, animals and human studies along with stimulatory effect on such cells to undergo apoptosis. The review also aim to further undertake wet lab studies regarding mechanisms by which Rosmarinic acid exert the said effects on various cancer models.

Index Terms:
Phytochemicals, Rosamarinic acid, oxidative damage, inflammation, apoptosis, cell cycle arrest

The term “Cancer” indicating a disease that can affect any part of the body gives dreaded thoughts to normal humans but renders thrills to scientific workers of the field of oncology and cancer biology. What defines cancer is the rapid creation of abnormal cells that has the ability to grow beyond usual boundaries and invade adjoining to distant body parts of the by a process called metastasis. Treatment cost of the disease might drain all economic resources of a common human being. The usual treatment regimes also impart numerous side

effects. Hence scientific workers throughout the globe are in constant search for cost effective herbal alternatives without much side effects.

There are several naturally occurring compounds that are shown to have the properties that can not only promote anticancer activity but also cause apoptosis and arrest of cell cycles (Aung et al, 2017). Some of the naturally occurring compounds of plant origin are phenolic compounds that contain at least one aromatic ring with one or more hydroxyl groups and are obtained from several fruits, vegetables, legumes, cereals, beer, coffee, wine and spices. These can be classified into different classes such as flavonoids, phenolic acids, phenolic alcohol, stilbenes and lignins according to their characteristics (Muller et al, 2019).

Amongst such phytochemicals, Rosmarinic acid (RA), a natural phenolic compound obtained mainly from the members of family Lamiaceae consists of several plants and herbs having medicinal importance. Numerous biological activities have been attributed to Rosmarinic acid that include antioxidant properties in form of Reactive Oxygen Species scavenger, lipid peroxidation inhibitor etc along with anti-inflammatory, neuroprotective and antiangiogenic activities (Elufioyea & Habtemariamb, 2019), (Noel et al, 2020), (Ouyang 2014). Scientific workers throughout the world have show antiviral, antibacterial and anti-mutagenic roles of Rosamarinic acid (Petersen, & Simmonds, 2003), (Yang et al, 2013); (Huang & Zheng , 2006) (Han, et al., 2015) (Han et al 2018).

Chemically Rosmarinic acid is an ester of caffeic acid and 3,4-dihydroxyphenyl lacticate and forms a major constituent of Chinese and oriental herbal medicines. Rosmarinic acid obtained from Rosemary (*Rosmarinus officinalis L.),* Basil *(Ocimumbasilicum),* Oregano *(Origanum vulgare),* Sage *(Salvia officinalis)* and *Melissa officinalis* has been shown to have desired pharmacological capacity in cancer treatment. Taking into account, the multidimensionality of Rosamarinic acid, it has been shown to have effect on several cell lines as well as cancer types. Numerous researches are being carried out in different parts of the globe whose findings appear to be engaging (Nunes , 2017). (Luo ,et al 2020) (Radziejewska et al 2021)

Han, et al., 2015 showed that treatment of Rosamarinic acid in MKN45 gastric cancer cells had effects on glycolytic pathways by way of suppression of glucose uptake as well as lactate production along with inhibition of expression of transcription factor, hypoxia-inducible factor-1α. Inflammation promoted the Warburg effect in cancer cells (Alfarouk KO, 2016). In connection to this, it was shown that Rosmarinic acid has the potential to suppress Warburg effect through inflammatory pathway involving interleukin IL-6/STAT3 stating its possible therapeutic action in gastric cancers (Han S et. al. 2015). More over it was also shown that Rosmarinic acid treatment brought about TNF-α-induced apoptosis through the suppression of NF-κB and reactive oxygen species in leukaemia U937 cells (Moon et. al, 2010).

Studies by Xu, Jiang et al, 2010 revealed that Rosmarinic acid treatment could inhibit the migration of MDA-MB-231BO bone-homing breast cancer cells mostly via the receptor activator of NF-κB ligand predicting the plausible anticancer potential of the said compound.

p53 is well-known tumor suppressor playing a vital role in the prevention of carcinogenesis (Liu, Cui et al, 2019). Bafna et al, 2010 demonstrated that MUC1 binds directly to the p53 regulatory domain and promoted transcription of growth arrest genes and brought about suppression of transcription of apoptotic genes. In connection to this, Radziejewska , et al, 2021 observed an increment of p53 expression as a result of Rosmarinic acid treatment in AGS gastric cancer cells where as anti-MUC1 did not enhance the effect generated by

Rosmarinic acid treatment. This brings a possible suggestion that Rosmarinic acid treatment could stimulate p53 independently from MUC1.

However in animal model studies such as in Ehrlich solid tumour mice, Rosmarinic acid treatment substantially suppressed growth of tumour with an increment in P53.

Additionally, Rosmarinic acid has been found to target numerous signalling pathways associated with breast cancer (Mahmoud, 2021). Rosmarinic acid treatment has been shown to induce early stage apoptosis in prostate cancer cell lines- PC-3 and DU145 cells as shown by Annexin V assay as well as late-stage apoptosis of prostate cancer cell lines- PC-3 and DU145 cells shown by TUNEL assay (Jang et al 2018).

Furthermore Jang et al 2018, also showed that Rosmarinic acid treatment in prostate cancer cell lines not only down regulates Proliferating cell nuclear antigen, cyclin D1 and cyclin E1 but also up regulates p21 and brings about modulation in the expression of components of apoptotic pathway-related genes such as Bax, caspase-3 etc which shows its high possibility as plant based anticancer therapeutic agent.

Leukaemia studies throughout the globe showed that Rosmarinic acid treatment inhibited CCRF-CEM and CEM/ADR5000 cells in dose-dependent manner bringing about low cytotoxicity to normal lymphocytes and caused by ameliorating cell adhesion to fibronectin and induced apoptosis and necrosis in a ROS-independent DNA damage and caspase-independent manner in the said cell lines (Wu, Hong et al, 2015).

Studies of Rosamarinic acid treatment on triple-negative breast cancer cell lines revealed its efficacy in terms of caused cytotoxic and anti-proliferative effects in the cell lines. Rosamarinic acid treatment in MDA-MB-231 cells brought about a cell cycle arrest in the G_0/G_1 phase whereas in MDA-MB-468 cells the cell cycle arrest was attributed in the S-phase leading to a twofold increase in the apoptosis induction (Messeha et al, 2020).

In continuation, animal model studies by Anusuya and Manoharan 2011, revealed the inhibitory effects of Rosmarinic acid against 7, 12-dimethylbenz (a) anthracene (a potent carcinogen found in tobacco) induced oral carcinogenesis in the buccal pouches of golden Syrian hamsters. Their studies showed prevention of the tumour formation and reversal of the biochemical and molecular markers suggesting the suppressive potential of Rosmarinic acid in oral carcinogenesis by way of promotion of the activities of enzymic and non enzymic antioxidants and down regulation of the expression of p53 and bcl-2.

Studies by Xavier et al, 2009 further revealed Rosmarinic acid induced apoptosis in human colon carcinoma derived cell lines having different mutations in signalling pathways where Rosmarinic acid treatment inhibited ERK phosphorylation.

Studies in human umbilical vein endothelial cells (HUVEC), Rosmarinic acid has been shown to inhibit steps of angiogenesis in a concentration-dependent manner along with the lowering of intracellular ROS levels resulting in the inhibition of ROS-associated VEGF expression and IL-8 release suggesting its anti-angiogenic potential (Huang & Zheng, 2010).

Zhang 2018 found that Rosmarinic acid treatment in OCVAR- 3 ovarian cancer cell lines has the potential of apoptosis induction, inhibition of cell migration and modulation of Lnc RNA Malat-1 expression causing cell shrinkage as well as loss of attachment with the surface of the plate. Rosamarinic acid treatment also brought

about condensation of chromatin and fragmentation of DNA along with suppression of migration of the cell proving its anticancer ability (Zhang 2018).

CONCLUSION

Rosmarinic acid is a dietary phenolic compound obtained from many culinary herbs, including rosemary perilla sage mint and tea and has been shown to possess numerous medicinal properties cobbling to cure multiple inflammatory diseases as well as cancer owing to its antioxidant properties and capability to arrest cell cycle and cause induction of apoptosis. Therefore, Rosmarinic acid has a potential to be used as a novel phytomedicine to act as a herbal or plant based cost effective chemotherapeutic agent with the anticipation to decrease the adverse side effects of the existing chemotherapeutic chemicals. Moreover, since few decades inflammatory diseases have been prevalent especially in developed and developing countries owing to the life style and industrial development (Xin et al., 2019).

Studies worldwide towards development of phytoformulations and Nutraceuticals have become necessary to reduce the costs and side effects of synthetic dietary and therapeutic substances such as Rosamarinic acid. In addition, physiological and supra-physiologic doses of the said phytochemical should be worked out to produce desired anti inflammatory and anti-cancer effects.

Of all retrieved articles, we found a deficit of clinical data of Rosamarinic acid treatment in case inflammatory diseases and cancers. Therefore, we mainly outlined the therapeutic potential of Rosamarinic acid against cancer in animal models, human subjects and cell line based studies in view to ascertain its plausible mechanisms of action in preclinical research. Further experimental studies are aimed so as to find out the dose and duration effects of Rosamarinic acid treatment to produce anticancer effects.

AUTHOR CONTRIBUTIONS

The authors have written and reviewed the manuscript and hence claim an equal authorship.

CONFLICT OF INTEREST

The authors declare no conflict of interest in presentation of the manuscript.

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