Review

Rosmarinic Acid: A Potential Therapeutic Agent in Gastrointestinal Cancers Management—A Review

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Rosmarinic Acid: A Potential Therapeutic Agent in Gastrointestinal Cancers Management—A Review

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Abstract: Gastrointestinal cancers are still the leading cause of death worldwide. This is related, among other things, to non-specific symptoms, especially in the initial stages, and also to limited possibilities of treatment. Therefore, research is still being conducted to improve the detection of this type of cancer and increase the effectiveness of therapy. The potential application of natural compounds in cancer management deserves special attention. In the group of such products there are polyphenolic compounds which reveal e.g. anti-oxidative, anti-carcinogenic, anti-inflammatory, anti-diabetic and neuroprotective properties. One of such polyphenols is rosmarinic acid, commonly found in plants such as Boraginaceae and Nepetoideae subfamilies of the Lamiaceae (mint) family, including *Origanum vulgare*, *Rosmarinus officinalis Thymus masticmasti chinaythia koreana*, *Ocimum sanctum*, and *Hyptis pectinate*. A number of studies considers the positive effects of rosmarinic acid in the treatment of many cancers, including gastrointestinal ones such as oral, stomach, pancreas, colon, and liver. The main aim of this paper was to focus on the summarized mechanisms of the action of rosmarinic acid in gastrointestinal cancers.

Keywords: gastrointestinal cancers; polyphenolic compounds; rosmarinic acid

1. Introduction

Cancers are one of the leading causes of incidence and mortality worldwide, especially when it comes to gastrointestinal ones which affect the digestive system. Generally, the cancers are considered as the major diseases affecting human health. The development of cancer process is provoked by genetic and environmental factors. It is estimated that about 50% of cancer events are caused by dietary habits and social behavior [1]. According to data prepared by the Global Cancer Observatory, the number of cancer deaths in the world in 2022 was approximately 9.7 million and the incidence was about 20 million. According to forecast data, it is estimated that the incidence rate by 2050 may increase to 35 million. The group of gastrointestinal cancers includes: oral, gastric, pancreas, colon and liver cancer. These cancers occupy the leading positions in terms of incidence and mortality of malignant tumors [2–4]. The reason is, that the most patients are diagnosed at the late stage of the disease due to the lack of characteristic symptoms of the disease at initial stages. Ongoing studies aim to enhance the detection and therapy outcomes of these types of cancer [5]. There are various treatment strategies for digestive tract tumors. These include surgery and postoperative adjuvant chemo and radiotherapy. Chemotherapy is a standard approach, but with serious limitations such as poor water solubility, low tumor targeting ability, adverse effects, and also chemoresistance. One more alternate choice of treatment seems to be immunotherapy. This has gained preference recently mainly because of its ability to alter the tumor microenvironment (TME) by supporting anti-tumor immune responses, improving the effectiveness of self-effector T cells, and antigen-presenting cells (APCs). Such treatment offers advantages like low side effects compared to other therapy modalities [6].

Due to the reasons mentioned above and also because of an increase in resistance of mammalian tumors towards existed anticancer drugs, there is a great need to develop alternative novel medications [7]. It is well known that diet can play a crucial role in cancers. Epidemiological studies

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indicated that decreased global cancer risks might be related to regular consumption of a high fiber, low fat diet followed by significant intake of vegetables and fruit [8].

Recently, special emphasis is placed on exploring the impact of natural compounds, particularly plant-derived polyphenols, on different stages of cancer development. Polyphenols are broadly present in beverages and food of plant origins (e.g. tea, wine, coffee, vegetables, fruit, species). They refer to wide group of plant secondary metabolites which can be small molecules or greatly polymerized big compounds. The quality and quantity of polyphenols in food depend on many factors such as plan genetics, growing conditions, harvest maturity or post-harvest handling [9]. Chemically, polyphenols are characterized by the presence of at least one phenol unit with one or more hydroxyl groups linked to it [10,11]. They represent a wide range of structural diversity and include phenolic alcohols, phenolic acids, and many more molecules with hydroxyl groups on aromatic rings [12]. Polyphenols play a crucial role in both plant biology and human health. They reveal wide, multifaceted bioactive properties. Polyphenolic compounds represent a promising and less invasive alternative to conventional treatment possibilities, with potential to augment the efficacy of standard therapeutic approaches [13–19].

The example of such compounds is rosmarinic acid (RA) representing low acute toxicity [20]. Its beneficial effects were revealed in the treatment of various cancers, including gastrointestinal, like oral, stomach, colorectal, pancreas and liver [21,28]. There have been also reports indicating gastro-protective effects of RA in ethanol-induced gastric lesions in vitro and in animal models [20,29]. Recently, several studies have revealed that rosmarinic acid was able to reverse cancer resistance to first-line chemotherapeutics, and also play a protective role against toxicity induced by chemotherapy and radiotherapy, mainly because of its scavenger capacity [30,31]. Thus, the main aim of the study was to present the summarized mechanisms of RA action in cancers mentioned above.

2. Rosmarinic Acid (RA)

2.1. Structure and Origin

Chemically, rosmarinic acid with molecular formula $C_{18}H_{16}O_8$ is polyphenolic compound, partly water-soluble ester of caffeic acid and 3,4-dihydroxyphenyl lactic acid with two catechol structures what gives molecular mass of 360 kDa (Figure 1). RA is widely present across over 160 species, commonly found in plants from Lamiaceae and Boraginaceae family, such as *Coleus scutellaroides*, *Lavandula augustifolia*, *Mellisa officinalis*, *Mentha* sp., *Origanum vulgare*, *Rosmarinus officinalis*, *Salvia* sp., *Satureja sp.*, *Thymus* sp., *Zataria multiflora* and *Zhumeria majdae.* These plants are very popular worldwide and are applied in everyday life in tea, herbs, cooking spices, vegetables and fruits [22,24,30,32,33]. For the first time, rosmarinic acid was successfully isolated in a pure form from rosemary (*Rosmarinus officinalis*) in 1958 [34].

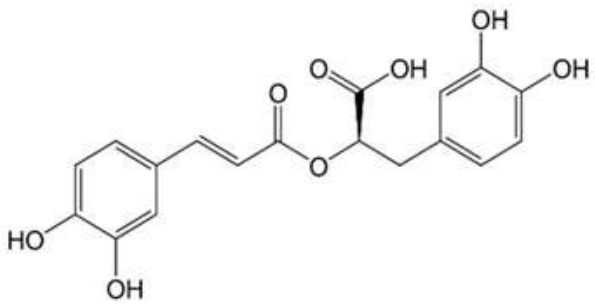

Figure 1. The structure of rosmarinic acid.

2.2. Preparation of Rosmarinic Acid

RA can be obtained in many ways. These include: heat extraction, ultrasound extraction and microwave extraction [32]. However, one of the most important methods of receiving rosmarinic acid and other polyphenolic compounds is the phenylpropanoid pathway [34].

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Initially, L-phenylalanine is transformed into t-cinnamic acid via phenylalanine ammonia lyase (PAL). Cinnamate 4-hydroxylyase, a cytochrome P450 monooxygenase, then converts t-cinnamic acid into 4-coumaric acid through hydroxylation at the 4-position. Coenzyme A ligase (4CL) acts on 4-coumaric acid to produce 4-coumaroyl-CoA, which serves as a donor for hydroxycinnamate in a compound derived from tyrosine. In the first step of L-tyrosine reaction, pyridoxal phosphate-dependent tyrosine aminotransferase (TAT) uses 2-oxyglutarate as a co-substrate, yielding the transaminated form of 4-hydroxyphenylpyruvic acid (pHPP) and glutamate. This stage marks the junction of rosmarinic acid, tocopherols, and plastoquinones biosynthesis. Hydroxyphenylpyruvate dioxygenase (HPPD) acts on 4-hydroxyphenylpyruvate, converting it into homogentisic acid, a precursor for tocopherols and plastoquinones. For rosmarinic acid biosynthesis, 4-hydroxyphenylpyruvate is converted by NAD(P)H-dependent hydroxyphenylpyruvate reductase (HPPR) into 4-hydroxyphenyllactic acid (pHPL), specifically the R (+) stereoisomer of hydroxyphenyl lactate. While HPPR can reduce 3,4-dihydroxyphenylpyruvate, it has low affinity. Alternatively, 3,4-dihydroxyphenylalanine (DOPA) can supply a 4-hydroxyphenyl lactate moiety. These two compounds, 4-coumaroyl-CoA and pHPL, are the final substrates for rosmarinic acid synthesis catalyzed by rosmarinic acid synthase (RAS). Through hydroxylation catalyzed by two cytochrome P450 monooxygenases, 4-coumaroyl-4'-hydroxyphenyllactic acid ester (4C-pHPL) is converted into rosmarinic acid [34].

2.3. General Action of Rosmarinic Acid in Tumor Prevention and Treatment

Rosmarinic acid displays a wide range of valuable, multifaceted, health-enhancing properties. There are many studies indicating that RA exerts anti-inflammatory, and anti-oxidant effects as well as inhibits cell proliferation, migration, adhesion, induces apoptosis, suggesting that it can be beneficial in preventing tumor growth and metastasis [27,28,30,35].

Oxidative stress is induced by the excessive gathering of free radicals which can be involved in variety of cancers development. It was reported that rosmarinic acid had the power to remove these free radicals by enhancing antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and non-enzymatic antioxidants [24,36]. Other authors demonstrated that the acid intensified Nrf2/HO-1 antioxidant system to downregulate NLRP3 and IL-1β in cancer cells [37]. In another studies, anti-inflammatory effects of RA were revealed by downregulation of COX-2, NF-kB, and ERK1/2 [24,38]. Moreover, Achour at al. proved inhibition of colorectal cancer development by rosmarinic acid action due to its antioxidant and anti-inflammatory effects [39]. It was also demonstrated that RA prevented tumor development via inhibition of DNA damage as a result of potential antioxidant ability of acid [40].

Cell cycle arrest and inhibition of proliferation were applied in the therapy of several cancers [24]. Rosmarinic acid was able to achieve such aims mostly by upregulation of p53, p21 and downregulation of cyclins D1, E, and B1 [41–44]. In other reports the authors revealed that RA was able to directly regulate cell proliferation-associated targets such as EGFR, MARK4, MCM7 [45–50].

Induction of apoptosis is one more excellent target in cancer therapy. Rosmarinic acid action was demonstrated to induce the expression of apoptosis-related factors such as Bax, caspase-3, caspase-8, and suppress the expression of anti-apoptotic proteins like Bcl-2 and PARP in different types of cancer cells [14,23,41,42,51,52]. It was also reported that PI3K/Akt and NF-kB signaling pathways were influenced by rosmarinic acid to induce apoptosis [14,53]. In the study carried out by Messeha et al., the authors revealed that RA stimulated apoptosis via upregulation of TNF and TNF receptor superfamily [54]. Moreover, another report demonstrated that rosmarinic acid combined with anti-MUC1 monoclonal antibody induced pro-apoptotic proteins such as p53, Bax, Bad, caspase-3, -8, and -9 [55].

It was revealed that epithelial mesenchymal transition (EMT), which is characteristic transformation occurring in invasive tumor cells, can be also affected by rosmarinic acid action. The acid inhibited EMT through upregulation of E-cadherin, downregulation of N-cadherin as well as by inhibition of MMPs activity. In such a way RA was able to impair invasive ability of cancer cells [23,52,56,57].

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To reduce invasion and metastasis of tumor cells is considered as one more important aim of cancer therapy. There are studies demonstrating the power of rosmarinic acid to inhibit these processes. Metalloproteinases of extracellular matrix facilitate invasion and metastasis. RA was observed to decrease cell invasive abilities by inhibition of MMP-2 and MMP-9 in several tumor cell lines [14,23,41,53]. Furthermore, tumor invasion ability was suppressed by the action of rosmarinic acid via decreasing of Akt phosphorylation and MMPs activity [46,52,56,57]. Apart from that, RA was demonstrated to inhibit cancer metastasis via VEGF and IL-8 signaling pathways [58–60] as well as by NF-kB ligand/TNF receptor superfamily member 11a/osteoprotegrin pathway [60].

Downregulation of glycolytic pathway can be also the goal of anticancer therapy. The Warburg effect attributes to glycolytic production of ATP and is considered as universal hallmark of the most cancer cells [61]. It was reported that rosmarinic acid suppressed the Warburg event through IL-6/STAT3 inflammatory pathway and inhibition of HIF-1α, a transcription factor affecting the glycolytic path [62,63].

In addition, some reports demonstrated the potential of rosmarinic acid to act as a chemosensitizer via modulation of specific signaling pathways. It is acknowledged that drug resistance is considered to be the main reason of chemotherapeutic treatment failure in many human tumors and is related to the type of cancer, stage, drug delivery, and individual condition of the patient [31,64]. For years, it has been indicated to combine natural products with traditional therapies [65]. It is due to these natural compounds can be active towards number of different molecular targets in cancer cells, impeding their growth and survival [66]. There are reports in which the authors stated that RA directly or indirectly intensified the potency of established anticancer drugs what resulted in an improvement of their therapeutic effects [31,45,67,68]. Because of the presence of two catechol moieties, rosmarinic acid creates polar molecule and due to this is able to penetrate lipid bilayers and save them from oxidation without changing their structure. Thus RA reveals pro-oxidant and antioxidant power. Antioxidant capacity of rosmarinic acid is strengthened by its ability to remove hydrogen peroxide and free radicals [27,69]. Such action enables RA to exhibit interactions with specific proteins known to be dysregulated in different cancer cells. In such a way rosmarinic acid reveals potency to augment the power of many chemotherapeutics against chemoresistance in these cells [31].

Nevertheless, despite of such promising results concerning rosmarinic acid action in different tumors, mechanisms underlying therapeutic activities of RA need further, wider investigations.

3. Rosmarinic Acid in Different Types of Gastrointestinal Cancer—Mechanisms of Action

3.1. Oral Cancer (OC)

The oral cancer is ranked among the most prevelent human cancers globally. The overall five-year survival rate of this cancer is much lower comparing to e.g. breast and prostate ones [41]. Since 2000, the incidence rate of this cancer has grown by 2% each year [70]. In the United States oral cancer is becoming one of the most common cancers [69].

Recently, rosmarinic acid has been studied as potential anticancer agent against human oral cancer cells. Luo et al. reported promising results demonstrating that RA was able to inhibit the proliferation of SCC-15 oral cancer cells. This antiproliferative effect was exerted via induction of apoptosis and arrest of cell cycle at G2/M phase. The ratio Bax/Bcl-2 apoptosis associated proteins as well as and caspase-3 protein were shown to increase under rosmarinic acid treatment. The mitotic cell cycle arrest occurred due to the decrease of cyclin B1 concentration caused by RA. Apart from that rosmarinic acid reduced the MMP-2 and MMP-9 protein concentrations [41].

3.2. Colorectal Cancer (CRC)

Colorectal cancers ranks as the third most frequent cancer by incidence and the second dominant cause of cancer-associated deaths. It was estimated, that in 2022 over 1.9 million new cases, and 904,000 deaths occured [2].

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Rosmarinic acid seems to reveal potential anti-cancer effects toward colorectal cancer acting on many steps of cancer development. Han et al. demonstrated that RA promoted cell death in metastatic CRC cells and suppressed their metastatic properties. It activated cycle arrest in the G0/G1 phase and apoptosis in colorectal cancer cells. Moreover, rosmarinic acid was able to inhibit metastatic potential of CRC cells, including epithelial mesenchymal transition (EMT), migration and invasion by activation of AMPK. RA modulated EMT by upregulation of an epithelial marker,E-cadherin, and downregulation of the mezenchymal markers, N-cadherin, snail, twist, vimentin, and slug. Apart from that rosmarinic acid supressed the expressions of MMP-2, -9, ICAM-1, and integrin β1 [23,34].

In HT-29 human colon cancer cells, RA treatment decreased N-cadherin expression and increased E-cadherin expression by TGFβ induction. It was also reported that rosmarinic acid inhibited the expression of MMP-1, -3, -9 and suppressed EMT through the p38 MAPK/AP-1 signaling. Inhibitory effect of RA on EMT was diminished by miR-1225-5p knockdown [56].

In another study carried by Jin et al., RA potency as anti-tumor factor in colitis-associated colon cancer (CAC) was evidenced. Rosmarinic acid was able to reduce colitis severity, inflammation-associated protein expression, tumor occurrence, and colorectal adenoma expansion. Moreover, it was observed that RA attenuated tumor growth via decreasing the expression of anti-apoptotic factors by inhibition of TLR4-mediated NF-kB and signal transducer and activator of transcription 3 (STAT3) [71,72].

Anticancer action of RA in HT-29 colon cancer cells was also demonstrated through inhibiting the expression of proinflammatory gene COX-2 which is considered as risk factor in cancer development. Moreover, the authors revealed that rosmarinic acid reduced AP-1 and the cellular levels of ERK1/2 activation [38,73].

In another study, the authors observed that RA with suppressory effect on COX-2, in combination with ginsenoside Rg1, had inhibitory outcome on the binding PD-1 and PD-L1, what resulted in further suppression of lung metastasis of colon cancer [74].

Targeting Warburg metabolism has been reported to be a promising method for the treatment of colon cancer [62]. Xu et al. studying colorectal carcinoma, found that rosmarinic acid supressed glucose consumption and lactate generation. The authors demonstrated also that RA reduced the expression of hypoxia-inducible factor-1α (HIF-1α) that influences the glycolytic pathway. Finaly it was concluded that rosmarinic acid could significantly regulate miR-155 and successively alter the IL-6/STAT3 signaling, resulting in the suppression of inflammation in the tumor microenvironment and the possible anti-Warburg effect [63].

Moreover, in another study the authors demonstrated that RA inhibited cell adhesion, migration, and invasion of Ls174-T human colon carcinoma cells mainly via extracellular signal-regulated protein kinases (ERK). Rosmarinic acid suppressed the activities of EGFR and VEGFR, and also inhibited nuclear translocation of NF-kB by pAkt and pERK de-phosphorylation. In addition, RA decreased the level of reactive oxygen species (ROS) and repressed the activity of metalloproteinase-2, -9. Interestingly, the authors claimed that rosmarinic acid with proper concentration had great anti-tumor and anti-metastatic abilities, similar to those represented by chemotherapeutic vinblastine [22,23,32,75].

Furthermore, RA administration diminished tumor formation, aberrant crypt foci multiplicity, and modified antioxidant status and oxidative stress markers in animal models of colorectal carcinoma induced by 1,2-dimethylhydrazine (DMH). Apart from that, rosmarinic acid attenuated the activities of fecal and colonic bacterial enzymes implicated in colorectal cancer progression. Upon such results, the authors proposed RA as chemopreventive agent [76,77].

Another study demonstrated that rosmarinic acid was able to induce apoptosis in HCT15 human colon carcinoma-derived cell line by inhibiting ERK phosphorylation [78]. Moreover, in another study Xavier et al. observed induced apoptosis caused by RA in human colon carcinoma-derived cell lines HCT15 and CO115, which have different mutations in the MAPK/ERK and PI3K/Akt signaling pathways. Rosmarinic acid reduced ERK phosphorylation in HTC15, but had no effect on Akt phosphorylation in CO115 cells [79].

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It was also revealed that RA from rosemary extract induced apoptosis and inhibited cell proliferation in HCT116 and SW480 colon cancer cell lines through the Nrf2/ARE signaling pathways [80].

3.3. Gastric Cancer (GC)

Yearly, about 990,000 individuals are identified with gastric cancer globally, with approximately 738,000 deaths. Thus, GC ranks as the fourth most commonly occuring cancer and the second leading cause of cancer-related deaths [1].

There are many reports demonstrating that gastric cancer development can be influenced by the action of rosmarinic acid. It seems to useful as pharmacological support for the prophylactic use to prevent gastric lesions [20]. Radziejewska et al. suggested usefulness of RA as a complementary agent supporting gastric cancer treatment. The authors revealed inhibitory effect of the acid on MMP-9 and TIMP-1 activity what was correlated with increased collagen type I expression. Rosmarinic acid decreased also the expression of tumor associated carbohydrate antigens – Tn, T, and sialyl Tn, as well as MUC1 mucin, the main carrier of mentioned antigens [81]. In another report, the authors demonstrated anti-cancer effects of RA alone and also in combination with anti-MUC1 monoclonal antibody in AGS gastric cancer cells. Applied treatment inhibited expression of cancer related sugar structures such as Tn, T, sialyl Tn, sialyl T, and fucosylated sugar antigens as well as expression of enzymes participating in their formation: ppGalNAcT2, C1GalT1, ST6GalNAcT2, ST3GalT1 and FUT4. Rosmarinic acid decreased also the expression of Gal-3 participating in metastasis [55].

In another study, Han et al. proposed that RA might be potentially a therapeutic agent for suppressing the Warburg effect in gastric carcinoma. The authors demonstrated that rosmarinic acid was able to inhibit glucose uptake and lactate production as well as inhibit HIF-1α suppression. RA was also able to decrease the expression of proinflammatory cytokines and miRNAs related to inflammation, suggesting that it may suppress the Warburg effect through an inflammatory pathway, such as the IL-6/STAT3 [61].

Another report suggested the potential of rosmarinic acid as a multidrug resistance-reversing factor in gastric cancer. The authors revealed that RA enhanced chemosensitivity of resistant SGC7901 gastric cancer cells to 5-Fu by downregulation miR-6785-5p and miR-642a-3p and increase FOXO4 expression. It was also observed that regulation of MDR-associated protein P-gp and pro-apoptotic Bax may as well be involved in this chemo-sensitizing action of rosmarinic acid [67].

Chen et al. reported that rosmarinic acid applied in SGC-7901 gastric cancer cells induced apoptosis through the mitochondrial pathway. It inhibited the cell viability, mobility and Bcl-2 expression. Oppositely, the apoptosis rate, Bax, cytochrome C, and cleaved caspase-3 expression were induced by RA action. Further, the authors suggested that gastric cancer cells could be induced by rosmarinic acid to arrest their cell cycle in the G0/G1 phase 822].

Recently, there have been attempts to synthetize RA analogues (RAAs) and apply them as anticancer drugs. In the study carried out by Li et al. the authors demonstrated promising results concerning RAA-11, synthetic analogue of rosmarinic acid, as the compound which was able to inhibit the growth, proliferation, and colony forming in SGC-7901 human gastric cancer cells. Apart from that it induced apoptosis by the EGFR/Akt/NF-kB pathway. Upon these results the author suggested RAA-11 as a potent agent for gastric cancer treatment [83].

3.4. Pancreatic Cancer (PC)

One more kind of cancer, which can be potentially influenced by rosmarinic acid is pancreatic cancer. In 2022, there were about 511,000 newly identified cases of PC and 467,000 deaths. Pancreatic cancer ranks as the sixth leading cause of cancer-associated deaths, accounting for just about 5% of global cancer fatilities [2]. PS mortality rate is very close to the incidence rate and about 90% of patients cannot be treated by surgery [84].

Zhou et al. proposed rosmarinic acid as an effective therapeutic agent in the treatment of pancreatic ductal adenocarcinoma (PDAC). The authors observed that RA induced G1/S cell cycle arrest as well as apoptosis by regulating the expression of P21, P27, CDK2, Cyclin E, Bax and Bcl-2. It

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was also revealed that the acid inhibited cells migration and invasion through E-cadherin and MMP-9. In addition, the authors demonstrated that rosmarinic acid suppressed the tumor growth presumably by inhibiting Gli1 in a proteasome-dependent manner [42].

In another study, the authors proposed rosmarinic acid as a promising candidate to inhibit human pancreatic cancer progression. They revealed a significant supression of cell growth, invasion, and migration by RA action. Further more, RA treatment triggered apoptosis and lowered the expression of EMT markers such as vimentin and N-cadherin [28].

In the studies performed by Han et al. the authors demonstrated that rosmarinic acid exerted supressing effects on cell viability, cell growth, invasion and migration, and epithelial mesenchymal transition as well as induced apoptosis of Panc-1 and SW1990 pancreatic cancer cell lines. It was suggested that such tumor inhibitory outcomes revealed by RA were achieved via regulating the miR-506/MMP2/16 signaling pathway [28,57].

3.5. Liver Cancer (LC)

Liver cancer is estimated to be the 6th most common cancer globally and is considered as the third leading cause-related deaths worldwide. In 2022, there were almost 865,000 newly diagnosed cases of liver cancer and about 757,000 deaths [2].

There are reports that liver cancer can be also affected by rosmarinic acid. An et al. observed that RA decreased proliferation rate, migration and invasion of HepG2 hepatoma cancer cells. The authors revealed also inhibitory effect of rosmarinic acid on MMP-2 and MMP-9 as well as inducing effect on apoptosis. Bcl-2 apoptosis supressor protein protein was downregulated, as Bax pro-apoptotic protein and cleaved caspase-3 was upregulated. Apart from that, it was reported that HepG2 metastasis was inhibited by RA via PI3K/Akt/NF-kB signalnig pathway [53].

Chen et al. demonstrated that rosmarinic acid had similar effect on SGC-7901 gastric cancer as on HepG2 liver cancer cells. Apoptosis was induced via mitochondrial pathway. Expression of anti-apoptotic Bcl-2 factor decreased, but Bax, cytochrome C, and cleaved caspase-3 increased. Liver cancer cells were induced by RA to arrest their cell cycle in S phase. In addition, the cell viability and mobility were also suppressed by rosmarinic acid action [82].

In another study, the authors also revealed similar anticancer potential of rosmarinic acid toward human HepG2 liver carcinoma cells. Induction of apoptosis exerted by RA activity was associated with the decrease of Bcl-2, increase of Bax levels, and activation of caspase-3 and -9. DNA fragmentation upon rosmarinic acid action was observed as well. Moreover, RA led to inhibit cell migration and invasion of liver cancer cells [85].

Wang et al. reported that rosmarinic acid suppressed the proliferation, invasion, and tumor growth in SMMC-7721 hepatocellular carcinoma cell line. The authors demonstrated G1 arrest and apoptosis induction. It was suggested that such effects were achieved by the inhibition of PI3K/AKT/mTOR signal pathway. They also revealed that RA could supress tumor formation of SMMC-7721 cells in vivo [86].

4. Conclusions

Scientists focus on significance of many herbal compounds in the treatment of many different types of cancers. As presented above, rosmarinic acid, commonly found in many medicinal plants, seems to be on of such promising agents which have the power to support treatment of cancers including gastrointestinal ones. Different signaling pathways can be affected by RA to reveal its anticancer potential (summarized in Figure 2). These research findings suggest that this acid is worth to be included in everyday diet. However, it is worth to emphasize that the effectiveness of such power of rosmarinic acid depends on intake, its stability, and bioavailability. The last factor for rosmarinic acid is quite low, mainly because of limited solubility in water, ineffective membrane permeability, high instability, and its potential interactions with numerous biological components in food. Therefore, the improvements of the dosage form and the development of chemical delivery systems are necessary for its antitumor applications [87]. Further preclinical and clinical studies seem to be crucial to thoroughly clarify its therapeutic power.

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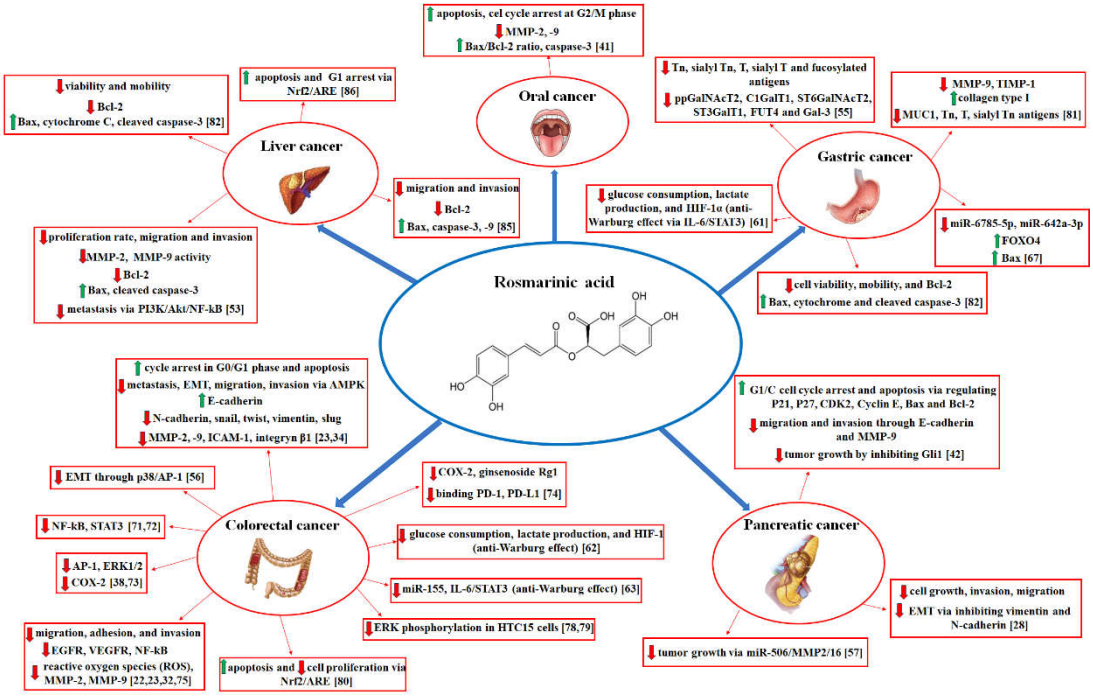

Figure 2. Summarized action of rosmarinic acid in oral, colorectal, pancreatic, gastric, and liver cancers.

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