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An overview of the chemistry and anticancer properties of rosemary extract and its diterpenes

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ABSTRACT

Rosemary (*Rosmarinus officinalis* L.), a culinary herb of the family Lamiaceae, has promising anticancer activity. This overview has updated the current knowledge on the chemistry and anticancer properties of rosemary extract, carnosic acid, carnosol, and rosmanol, focusing on colon and prostate cancer cells since they are the most susceptible. The information was procured from Google, Google Scholar, PubMed, PubMed Central, Science Direct, J-Stage, and PubChem. Phenolic compounds isolated from the aerial parts of *R. officinalis* are flavonoids, phenolic acids, diterpenes, triterpenes, terpenoids, and phenylpropanoids. Some of the compounds are new to science, to the genus, and to the species. Almost 30 compounds possess anticancer properties. Rosemary extracts contain abietane diterpenes, with carnosic acid, carnosol, and rosmanol being the most common. Their molecular structures are similar to three fused aromatic rings. Carnosic acid has a –COOH group at C20, carnosol has a lactone ring occurs across the B ring, and rosmanol has a –OH group at C7. Against colon and prostate cancer cells, the rosemary extract and diterpenes inhibited cell viability and induced apoptosis and G2/M phase cell cycle arrest. The inhibition of cell migration and adhesion has also been reported. The rosemary extract and diterpenes also inhibited colon and prostate cancer xenograft in mice. Rosemary extract is more cytotoxic than the diterpenes due to its polyphenols such as flavonoids and triterpenes. *In vitro* and *in vivo* cytotoxic activities involve different molecular targets and signalling pathways. Some prospects and areas for future research are suggested.

Implication for health policy/practice/research/medical education:
This overview is on the chemistry and anticancer properties of extracts and diterpenes (carnosic acid, carnosol, and rosmanol) of rosemary. Emphasis is on colon and prostate cancer cells. There is convincing scientific evidence that carnosic acid and carnosol are promising anticancer agents. Prospects for further research are promising.

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Introduction

Diterpenes are C20 compounds that depending on their core skeleton are classified as linear, bicyclic, tricyclic, tetracyclic, pentacyclic, or macrocyclic compounds (1). They have attracted growing research interest due to their interesting biological activities and pharmacological properties. Abietane diterpenes or abietanes, found in rosemary, are tricyclic diterpenoids characterized by three fused six-membered rings and alkyl functional groups at carbons 4, 10, and 13 (2). Out of 13 000 diterpenes reported from plants, ~3000 are from Lamiaceae, commonly known as the mint family that include the widely used aromatic and culinary herbs e.g., rosemary, sage, and thyme (3).

Lamiaceae is a large family of flowering plants, consisting of 250 genera and 7852 species (4). The original family name was Labiatae because flowers have petals that are fused into top and bottom lips (5). Currently, most botanists use Lamiaceae as the family name. Species of the family have many medicinal, culinary, and ornamental uses worldwide, and many biologically active essential oils have been isolated (6).

Cancer along with cardiovascular disease are the leading causes of premature death in 127 countries worldwide (7). In Global Cancer Statistics (GLOBOCAN) 2020, produced by the International Agency for Research on Cancer, new cancer cases were 19.3 million, and cancer death was 10.0

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million (8). Lung (11.4%) and breast (11.7%) cancers remained the leading cause of cancer death, followed by colon (9.8%), prostate (7.3%), stomach (5.6%), and liver (4.7%) cancers. In Cancer Statistics 2020, prepared by the American Cancer Society, the number of new cases and death in the United States were 5.8% and 8.8% for colon cancer, and 10.6% and 5.5% for prostate cancer, respectively (9). Most cases of colon cancer (4%–5%) are detected in Western countries and the risk is associated with age, chronic disease history, and lifestyle (10). The majority of prostate cancer is diagnosed in older men, and as the population ages increase, the number of prostate cancer cases is elevated (11).

The anticancer properties of rosemary extract, carnosic acid, carnosol, and rosmanol are focused on colon and prostate cancer cells because they are the most susceptible. Their cytotoxic activities involve the growth inhibition of cancer cells, multiple molecular targets, and various signalling pathways. Growth inhibition entails apoptosis, antiproliferation, and inhibition of cell migration. This overview is on the botany, chemistry, and anticancer properties of rosemary extract and its principal diterpenes, namely, carnosic acid, carnosol, and rosmanol.

Botany and uses of rosemary

Rosmarinus officinalis L. (Rosemary), a culinary herb of the family Lamiaceae, is native to the Mediterranean region and cultivated worldwide. The plant grows in dense thickets of up to a meter in height (12,13). Leaves are evergreen, sessile, opposite, leathery, and linear in shape (Figure 1). The upper surface is dark green, while the lower surface is covered with tomentous and has a prominent midrib. Leaves emit a characteristic aroma when crushed. More than 20 varieties of rosemary have been identified (14). Flowers are light blue (most common), white, or pink with petals fused into the top and bottom lips (Figure 1).

Rosemary is an aromatic herb that is widely used for food flavouring and preservation. The species has been named the Herb of the Year in 2001 by the International Herb Association (13). In 2008, the European Food Safety Authority (EFSA) of the European Union approved the use of standardized rosemary extracts as a food additive (15). It is also an ornamental and medicinal plant. In traditional medicine, rosemary is used for its analgesic, antibacterial, anti-inflammatory, astringent, carminative, digestive, diuretic, and wound healing properties (14,16). The essential oil of rosemary is used to treat wounds, rashes, headaches, dyspepsia, circulation problems, and as an expectorant, diuretic, and antispasmodic. Rosemary has also been reported to exhibit anticancer, antidiabetic, antimicrobial, anti-inflammatory, antiobesity, antioxidant, antihyperglycaemic, antihypertensive, antithrombotic, diuretic, and hepatoprotective properties (17,18).

Figure 1. Leaves and flowers of rosemary.

Phytoconstituents of rosemary extracts

From the aerial parts of *R. officinalis*, flavonoids (37), diterpenes (20), phenolic acids (11), triterpenes (10), terpenoids (6), and phenylpropanoids (2) have been isolated and identified (Table 1). Compounds new to science included officinoflavonosides A & B (19), and officinoterpenosides A1, A2 & B–D (20). New to the genus *Rosmarinus* include tiliadin and 5,7,4′-trihydroxy-3′-*O*-β-D-glucuronic acid-6″-methyl ester (19). A total of 38 compounds are new constituents of rosemary. Compounds that are most often isolated included carnosic acid, carnosol, and rosmanol (diterpenes), genkwanin (flavonoid), betulinic acid (triterpene), and rosmarinic acid (phenolic acid) (Table 1. Their chemical structures are shown in Figure 2. Triterpenes and diterpenes are dominant in the extracts of rosemary with contents of 122 and 109 mg/g, respectively, compared to flavonoids (5.2 mg/g) (21).

Flavonoids in rosemary are mostly flavones, comprising apigenin, diosmetin, genkwanin, hispidulin, and luteolin (Table 1). Rosmarinic acid and caffeic acid are common phenolic acids. The main components of rosemary essential oil are 1,8-cineole, α-pinene, camphor, camphene, β-pinene, borneol, and limonene (5).

Triterpenes (12.2%) and diterpenes (10.9%) are the dominant classes of compounds of rosemary (21). Major triterpenes are ursolic acid, betulinic acid, and micromeric acid (Table 1). The most common diterpenes are carnosic acid, carnosol, and rosmanol. The concentration of carnosic acid and carnosol of rosemary was 23 and 2.4 mg/g in fresh leaves and 42 and 3.9 mg/g in dried leaves, respectively (23). As a comparison, the concentration of carnosic acid and carnosol in fresh leaves of sage was 12 and 1.7 mg/g, respectively. From rosemary extracts, the contents of carnosic acid, carnosol, and rosmanol have been reported to be 121, 29, and 1.3 mg/mL (16), and 83, 10, and 4.4 mg/g (21), respectively.

Diterpenes of rosemary

The chemical structures of carnosic acid, carnosol, and rosmanol are shown in Figure 3. They are abietane

Table 1. Important compounds isolated from the aerial parts of *Rosmarinus officinalis*

Compound type	Compound name	Reference
Flavonoids	+ Acacetin ○	(19)
	+ Apigenin	(21-25)
	Apigenin-7-*O*-β-D-lutinoside ○	(19)
	Circiliol ○	(21)
	Circimaritin BL	(21,23-26)
	6''-*O*-(*E*)-*p*-Coumaroylnepitrin	(19,27)
	+ Diosmin ○	(28)
	+ Diosmetin	(21,23,24)
	+ Eriocitrin ○	(28)
	6''-*O*-(*E*)-feruloylhomoplantaginin ○	(27)
	6''-*O*-(*E*)-feruloylnepitrin	(19,27)
	Gallocatechin ○	(21)
	+ Genkwanin	(21,23,24,26-29)
	+ Hesperidin	(16,26,28)
	+ Hispidulin	(21,23-25,29)
	Homoplantaginin	(19,28,29)
	6-Hydroxyluteolin-7-glucoside	(19,26)
	+ Isorhamnetin ○	(16)
	Isorhamnetin-3-*O*-hexoside ○	(29)
	Isoscutellarein 7-*O*-β-D-glucoside ○	(28)
	+ Kaempferol ○	(27)
	Ladanein ○	(27)
	+ Luteolin	(16,27,29)
	Luteolin 3'-*O*-(3''-*O*-acetyl)-β-D-glucuronide	(19,27,28)
	Luteolin 3'-*O*-(4''-*O*-acetyl)-β-D-glucuronide	(19,28)
	Luteolin 4-*O*-β-D-glucoside ○	(16)
	Luteolin 7'-*O*-β-D-glucoside ○	(19)
	Luteolin 3'-*O*-β-D-glucuronide	(19,26-28)
	Luteolin 7'-*O*-β-D-lutinoside ○	(19)
	6-Methoxyluteolin 7-*O*-β-D-glucopyranoside ○	(27)
	+ Naringin ○	(25)
	Nepetrin	(19,26)
	Officinoflavonosides A, B *	(19)
	+ Rutin ○	(16)
	Tiliadin ●	(19)
	+ Vitexin ○	(16)
Phenolic acids	+ Asiatic acid ○	(26)
	+ Caffeic acid	(16,22,25)
	+ Ferulic acid ○	(22)
	1-*O*-Feruloyl-β-D-glucopyranose ○	(27)
	1-*O*-(4-Hydroxybenzoyl)-β-D-glucopyranose ○	(27)
	+ Quinic acid ○	(26)
	+ Rosmarinic acid	(16,25-27,29)
	Rosmarinic acid-3-*O*-glucoside ○	(26)
	+ Syringic acid ○	(26)
	5,7,4'-Trihydroxy-3'-*O*-β-D-glucuronic acid-6''-methyl ester ●	(19)
	+ Vanillic acid ○	(25)
Diterpenes	+ Carnosic acid	(16,21,23-27,29)
	Carnosic acid glucuronide ○	(23)
	Carnosic acid sulphate ○	(23)
	+ Carnosol	(16,21,23,24,26,27)
	Carnosol glucuronide ○	(23)
	Carnosol isomer	(23,24,26)
	Epiisorosmanol	(23,24,26)
	Epirosmanol	(20,21,23,24,26)
	Epirosmanol methyl ether ○	(26)
	+ Hinokiol ○	(21)
	Isorosmanol	(20,29)
	12-Methoxycarnosic acid	(16,21,23,24,26)
	7-Methoxyrosmanol ○	(20)
	Methyl carnosate ○	(29)

Table 1. Continued

Compound type	Compound name	Reference
	+ Miltipolone	(21,23,24)
	Rosmadial	(21,23,24,26,29)
	+ Rosmanol	(20,23-26)
	Rosmanol glucuronide ○	(23)
	Rosmanol isomer ○	(29)
	Rosmaridiphenol	(21,23,24,26,29)
Triterpenes	Anemosapogenin	(21,23,24,26)
	Asteryunnanoside B ○	(20)
	Augustic acid	(23,24,26)
	Benthamic acid	(21,23,24,26)
	Glucosyl tormentate ○	(20)
	Micromeric acid	(20,21,23,24,26)
	Niga-ichigoside F1 ○	(20)
	+ Betulinic acid	(16,21,23,24,26,29)
	+ Oleanolic acid	(20,29)
	+ Ursolic acid	(20,21,23,24,26,29)
Terpenoids	5-Exo-hydrocamphor 5-*O*-β-D-glucopyranoside ○	(20)
	Officinoterpenosides A1, A2, B–D *	(20)
Phenylpropanoids	[9]-Shogaol	(21,24)
	[9]-Shogaol isomer	(24,26)

* Compounds new to science, ● First isolated from the genus *Rosmarinus*, ○ First isolated from *Rosmarinus officinalis*, + Compounds with anticancer properties.

diterpenes containing 20 carbons and consisting of three fused rings, of which ring C is aromatic (2). Two –OH groups are attached to C11 and C12 of ring C, while four $-CH_3$ groups are attached to C16 and C17 of ring C, and to C18 and C19 of ring A.

Carnosic acid (salvin) was first discovered by Linde in sage (2). It has a molecular formula of $C_{20}H_{28}O_4$ and a molecular weight of 332.4 g/mol and has a –COOH group at C20 (30). Because of its *o*-diphenol structure (catechol) at ring C, carnosic acid is unstable and gets converted to carnosol and rosmanol upon oxidation (30-32). Carnosic acid possesses pharmacological properties such as antiadipogenic, antiangiogenic, antiatherosclerosis, antidiabetic, anti-inflammatory, antimicrobial, antioxidant, antiplatelet, antitumor, hypolipidemic, and neuroprotective activities (33,34).

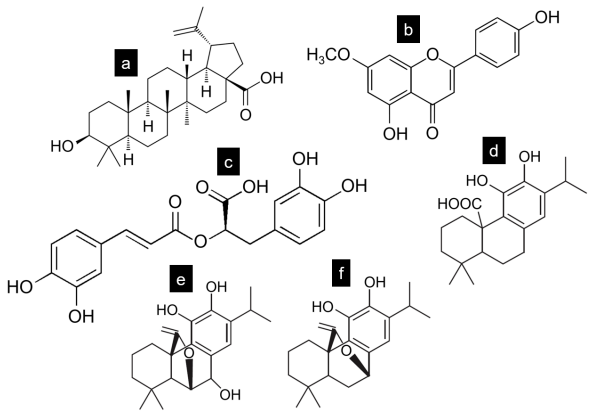

Figure 2. Chemical structures of compounds that are most often isolated from rosemary. a: Betulinic acid, b: Genkwanin, c: Rosmarinic acid, d: Carnosic acid, e: Rosmanol, f: Carnosol

Carnosol (pikrosalvin) has a lactone ring that occurs across the B ring between C7 and C20 (35-37). Carnosol is a product of oxidative degradation of carnosic acid, and has a molecular formula of $C_{20}H_{26}O_4$ and molecular weight of 330.4 g/mol. Among the pharmacological properties of carnosol are antiangiogenic, anti-

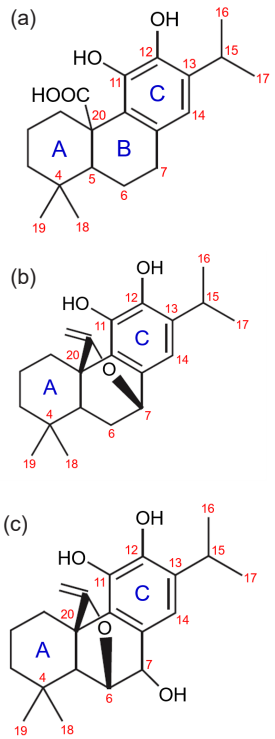

Figure 3. Labelled chemical structures of carnosic acid (a), carnosol (b), and rosmanol (c).

inflammatory, antimicrobial, antioxidant, antitumor, and gastroprotective activities (34,36).

Rosmanol has a lactone ring that occurs across the B ring between C6 and C20 and an –OH group at C7. Its molecular formula is $C_{20}H_{26}O_5$ and its molecular weight is 346.4 g/mol (38). Rosmanol can easily be transformed from carnosic acid by oxidation and has been synthesized from carnosol by introducing an oxygen atom at C7 (39). The procedure of synthesis involved treating carnosol in acetone with aqueous sodium bicarbonate (5%) at room temperature for 6.5 hours (39). Rosmanol possesses antioxidant and anti-inflammatory properties (40,41).

Rosemary and colon cancer

Against HGUE-C-1, SW480, and HT-29 colon cancer cells, cytotoxic effects of rosemary extracts at 48 hours were significantly stronger than those at 24 hours (21). HT-29 cells were most resistant to the extract and longer treatments yielded lower IC_{50} values. The cytotoxicity of six methanol rosemary extracts was tested using five different cancer cell lines (42). Against DU-145 colon cancer cells, extract I-SC displayed the strongest activity with a half-maximal inhibitory concentration (IC_{50}) value of 8.8 μg/mL, attributed to the high content of carnosic acid (50 mg/g extract). When the cytotoxicity of an enriched rosemary extract was tested against HCT116 and HT-29 colon cancer cells, the IC_{50} values were 11–12 and 22–32 μg/mL, respectively (43). The enriched rosemary extract contained 264 and 34 mg/g extract of carnosic acid and carnosol, respectively.

HCT116 cells treated with carnosic acid for 24, 48, and 72 hours had IC_{50} values of 27, 28, and 29 μM, respectively (44). In an animal study, carnosol administered in the diet inhibited colon cancer cells at the initiation, promotion, and progression stages, besides reducing intestinal tumor multiplicity (45,46). A study on rosmanol showed that the diterpene strongly induced apoptosis in COLO 205 colon cancer cells with a 51% apoptotic ratio and IC_{50} value of 42 μM (47). The anticancer effects and mechanisms of rosemary extracts, carnosic acid, carnosol, and rosmanol towards colon cancer cells are summarized in Table 2.

Growth inhibition of SW620 and DLD-1 colon cancer cells by the rosemary extract was greater than carnosic acid or carnosol alone or in combination, suggesting that compounds other than carnosol and carnosic acid present in rosemary extract also contributed to its anticancer effects (49). Proteomic profiling of the effects of carnosic acid and carnosol in the rosemary extract on HT-29 colon cancer cells showed that these two diterpenes induced different Nrf2-mediated responses (61).

Similarly, carnosic acid and other polyphenols in the rosemary extract inhibited the viability of HT-29 and SW480 colon cancer cells but were not as potent as the extract (21). Among the other polyphenols, rosmarinic acid is a likely candidate contributing to cell growth inhibition. The cytotoxic effects of rosmarinic acid include HT-29 (62), HCT15, CO115 (63,64), and Ls174-T (65) colon cancer cells. Other rosemary extract polyphenols with cytotoxic activities include triterpenes such as betulinic acid and ursolic acid. The anticancer property of betulinic acid is associated with its ability to induce cancer cell death by triggering the mitochondrial pathway of apoptosis (66). Ursolic acid induces apoptosis and inhibits proliferation and angiogenesis in breast and colon cancer cells (67).

Rosemary and prostate cancer

Rosemary extracts are known to inhibit the proliferation of prostate cancer cells. Ethanol extracts of rosemary collected from four regions of Morocco displayed antiproliferative effects towards LNCaP prostate cancer cells with comparable IC_{50} values of 14.2–15.0 μg/mL (18). When tested against 22Rv1 and LNCaP prostate cancer cells and prostate epithelial cells, a standardized rosemary extract significantly modified ER stress in the cancer cells but not in the epithelial cells. There was a decrease in androgen receptor expression, possibly regulated by ER stress proteins. Using a prostate cancer xenograft, athymic nude mice that were orally given the rosemary extract had 46% less tumor growth and 26% less serum prostate-specific antigen (PSA) levels than the control group (69).

Recently, treatment of androgen-insensitive PC-3 prostate cancer cells with rosemary extract reduced cell proliferation, survival, and migration by targeting Akt and mTOR signaling (70). Treatment of androgen-sensitive 22RV1 prostate cancer cells with rosemary extract reduced cell proliferation and survival while the extract had no effect on normal prostate epithelial PNT1A cells.

The anticancer properties of carnosic acid and carnosol towards prostate cancer cells have been reviewed (71). Carnosic acid, at 80 μM, induced 56% and 47% apoptosis in PC3 and DU-145 prostate cancer cells, respectively (72). Carnosic acid was found to trigger apoptosis in PC3 prostate cancer cells *via* inhibition of the phosphatidylinositide 3-kinase (PI3K)/Akt signalling pathway, and suppression of the IκB kinase (IKK)/nuclear factor kappa B (NF-κB) pathway. Molecular mechanisms involved the inhibition of caspases 8 and 9, and the activation of caspases 3 and 7 (72). Therefore, there is strong evidence for the involvement of caspases in the apoptotic effects of carnosic acid on prostate cancer cells.

Carnosol inhibited tumor cell proliferation and induced apoptosis in PC3 prostate cancer cells by inducing G2/M phase cell cycle arrest and targeting the adenosine monophosphate-activated protein kinase pathway (73). Athymic nude mice given carnosol orally had 46% less tumor growth and 26% less serum PSA levels than the control group (74). This study highlighted the unique property of carnosol, functioning as a dual disruptor of AR and ER activity in athymic nude mice implanted

Table 2. The mechanisms of anticancer effects of rosemary on colon cancer cells

Rosemary	Cell line	Anticancer effect and mechanisms	Reference
Extract	HGUE-C-1, HT-29 & SW480	Antiproliferative effects of cancer cells by extract were attributed to the pro-oxidative properties, which increased the intracellular generation of ROS and upregulation of the Nrf2 pathway.	24
	SW620 & DLD-1	The extract reduced cell viability and proliferation and promoted apoptosis by upregulation of PARP cleavage.	48,49
	SW620 xenograft	The antitumor mechanism in athymic male nude mice involved the upregulation of GCNT3 and the downregulation of miR-15b.	49
	HT-29 & SW480	The extract inhibited cell proliferation and promoted cell cycle arrest by modulating Nrf2 and ER stress.	50
	HT-29	The extract inhibited cell proliferation and promoted cell cycle arrest and autophagy *via* accumulation of ROS, increase in H_2O_2, enhancement of ER stress, and upregulation of the Nrf2 pathway.	51,52
	HCT116 & SW480	The extract induced apoptosis and reduced cell viability by activating caspase 3 and upregulating the expression of Nrf2 and sestrin-2 *via* the PERK pathway.	53
	HT-29 xenograft	Athymic male nude mice, orally administered with extract, displayed ROS-related necrotic cell death and less tumor growth.	54
	Colon cancer xenograft	The extract reduced colon cancer xenograft in male Sprague-Dawley rats *via* the downregulation of β-catenin, K-ras, and cmyc gene expression levels.	55
Carnosic acid	HCT116	Carnosic acid triggered cell apoptosis by the generation of ROS, induction of p53 and Bax, activation of caspases, and inhibition of the STAT3 signalling pathway.	44
	HCT116 & SW480	Carnosic acid induced apoptosis and decreased cell viability by activating caspase 3 cleavage and inducing the expression of Nrf2 and ER stress *via* the PERK pathway.	53
	Caco-2, HT-29 & LoVo	Carnosic acid induced apoptosis and inhibited cell migration and adhesion by the downregulation of COX-2 and reduction of uPA and MMP -2 and -9.	56
	HT-29	Carnosic acid attenuated cell proliferation, induced cell cycle arrest, and triggered apoptosis *via* attenuation of leptin receptor signalling and downstream inhibition of Akt and ERK phosphorylation.	57
	CaCo-2	Carnosic acid inhibited cell growth *via* cell cycle arrest at G2/M phase by reducing cyclin A and increasing cyclin B1 levels.	58
Carnosol	CaCo-2	Carnosol inhibited cell growth *via* cell cycle arrest at G2/M phase by a reduction in cyclin A and increase in cyclin B1 levels.	58
	HCT116	Carnosol induced apoptosis of cancer cells *via* the generation of ROS, induction of p53, activation of caspases 9 and 3, and inhibition of STAT3 signalling.	59
	HCT116 & SW480	Carnosol inhibited cell growth by activation of PERK and Nrf2 and induction of sestrin 2.	60
Rosmanol	COLO 205	Carnosol induced apoptosis by caspase activation and the regulation of mitochondrial apoptotic and death receptor pathways.	47

Bax = Bcl2-associated X protein, COX = cyclooxygenase, ER= endoplasmic reticulum, ERK = endoplasmic reticulum kinase, GCNT3 = glucosaminyl (N-acetyl) transferase 3, H_2O_2 = hydrogen peroxide, Nrf2 = nuclear factor erythroid 2-related factor 2, MMP = matrix metalloproteinase, PARP = poly-(ADP)-ribose polymerase, ROS = reactive oxygen species, PERK = PKR-like endoplasmic reticulum kinase, uPA = urokinase plasminogen activator, STAT3 = signal transducer and activator of transcription 3.

with prostate cancer cells. There are no reports on the anticancer properties of rosmanol towards prostate cancer cells.

Rosemary and other cancers

Rosemary extracts are cytotoxic to bladder, breast, cervical, leukemia, liver, lung, ovarian, and pancreatic cancer cells (17). Carnosic acid is cytotoxic to the brain, breast, kidney, leukemia, liver, lung, neural, oral, ovarian, pancreatic, renal, and skin cancer cells (75). Carnosol is cytotoxic to breast, liver, ovarian, and skin cancer cells (35,36).

A recent review reported the *in vitro* anticancer activities of rosemary extracts on liver, lung, and breast cancer, including leukemia, carnosic acid on skin and breast cancers, including leukemia, and carnosol on skin cancer. The *in vivo* anticancer activities of rosemary extracts have also been reported on the liver, skin, and breast cancers, carnosic acid on the skin and breast cancers, and carnosol on oral cancers (76). From this review, it can be deduced that the ranking of anticancer activities is as follows: rosemary extracts > carnosic acid > carnosol.

Recent studies have reported the cytotoxicity of rosemary extracts on breast cancer (70,77). Carnosic acid is cytotoxic to lung (78,79), gastric (80), and liver cancer cells (81). Carnosol and rosmanol are cytotoxic to liver cancer cells (81) and breast cancer cells (82), respectively.

Chemopreventive benefits of rosemary

Rosemary has the chemopreventive benefits of enhancing

the antitumor effect of anticancer drugs and of reversing the multidrug resistance of cancer cells. The antitumor efficacy of 5-fluorouracil in both drug sensitive and resistant colon cancer cells was enhanced by the rosemary extract (48). It is, therefore, possible that the rosemary extract can be used as a complementary agent in cancer therapy.

Phytochemicals in rosemary are natural and are considered safe for consumption. Compounds such as diterpenes and triterpenes are rich in antioxidants and are promising dietary chemopreventive agents. In the presence of carnosic acid as low as 10 μM concentration, KB-C2 oral epidermal carcinoma cells were more susceptible to the cytotoxicity of vinblastine (83,84). This demonstrates that carnosic acid has chemo-sensitizing effects by reversing P-glycoprotein-mediated multidrug resistance and by increasing the intracellular accumulation of the anticancer drug. An earlier study demonstrated that constituents of rosemary extracts inhibited P-glycoprotein activity in multidrug-resistant MCF-7 breast cancer cells (85). These studies affirmed the benefits of rosemary as a promising dietary chemopreventive agent by complementing the efficacy of anticancer drugs and reversing multidrug-resistance of cancer cells.

Conclusion

This overview summarised the chemistry and anticancer properties of the rosemary extract and its diterpenes. Phytochemical studies are rewarding as they still yield compounds that are new to science, to the genus *Rosmarinus,* and to the species *R. officinalis*. Almost 30 compounds in rosemary possess anticancer properties. Descriptions of the cytotoxic activities and the molecular mechanisms of the rosemary extract and its diterpenes are focused on colon and prostate cancer cells. Among the three diterpenes, the role of rosmanol in cancer antiproliferation and prevention is the least studied. Overall, there is convincing scientific evidence that carnosic acid and carnosol are promising anticancer agents. However, further research is warranted to evaluate the safety and efficacy of these diterpenes when applied alone or in combination with other chemotherapy agents. There is a dearth of knowledge regarding their pharmacokinetics, bioavailability, and reversal in multidrug resistance. Other research includes the standardization of rosemary extracts for comparative studies, and structural modifications of these diterpenes to yield derivatives having enhanced cytotoxic activities. Knowledge of these aspects is meagre. More systematic animal studies are needed before clinical trials using human subjects can be initiated.

Authors' contribution

EWCC conceived the idea. HTC and SKW collated articles from databases, analyzed their information, drafted the manuscript, and prepared the table and figures. The manuscript was finalized by EWCC and HTC. EWCC, the corresponding author, completed, submitted and revised the manuscript, and paid the publication fee.

Conflict of interests

The authors declare no conflict of interest.

Ethical considerations

All ethical issues have been carefully observed by authors.

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