Review Article

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Studies with *Myrtus communis* L.: Anticancer properties

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ABSTRACT

Myrtus communis (MC) L. is a well-known Mediterranean plant with important cultural significance in this region. In ancient times, MC was accepted as a symbol of immortality. Maybe due to this belief, it is used during cemetery visits in some regions. Although it is a well-known plant in cosmetics, and there is a lot of studies about its different medical properties, anticancer studies performed using its different extracts or oils are not so much, but increasing. We collected these anticancer property-related studies in this review.

KEY WORDS: Myrtucommulone, *Myrtus communis*, new drug development

Cancer is a group of diseases which are characterized by uncontrolled growth and spread of abnormal immortal cells, and its causes may be both external and internal factors. Cancer is a very important health problem, because its frequency is increasing every day, and there is no satisfying medical treatment method available today [1]. Although cancer is one of the most-studied diseases all around the world, it looks like that the main source of hope is natural, and especially plant derived, products. Because natural or natural-derived products have been the most significant source of drugs in modern medicine and dominant role of these natural products in cancer is obvious with about 74% of anticancer compounds being natural products, or natural product-derived products [2]. Probably, heavy screening and goal-oriented detailed scientific research would be the most distinctive steps in determining and developing potentially "druggable" targets in cancer research [2,3].

Myrtus communis L. (MC) is an evergreen shrub with a height of about 1-5 m, and probably the only myrtle variety that has an important cultural significance in Mediterranean region and Anatolia [4]. Besides its cultural importance, MC has a lot of medical usages in different indications such as diarrhea, peptic ulcers, hemorrhoids, inflammation, bleeding, headache, palpitation, leucorrhoea, urethritis, epistaxis, conjunctivitis, excessive perspiration, cough, pulmonary and skin diseases, diabetes mellitus, antiseptic, pain, heartburn, swelling, stiffness of the limbs, to remove mucus from the chest [4-7]. There are also some information about the usage of MC for anticancer purposes in traditional medicine [3,6,8]. Anticancer properties of MC were previously investigated in a number of studies, and in some of these studies myrtucommulone which is a unique, nonprenylated acylphloroglucinol, was found to be an active compound [9]. Myrtucommulone has antioxidant, antibacterial, anti-inflammatory, anti-diabetes, and anticancer properties, and it is found in the leaves of MC [5-7,9-20] [Table 1].

STUDIES ABOUT ANTICANCER PROPERTIES OF MC L

Alwan *et al*. showed that ethanolic extract of MC inhibited aryl hydrocarbon hydroxylase (AHH) activity and ^{3}H-benzo(a) pyrene (^{3}H-BP) binding to rat liver microsomal protein, effectively. In the same study, no inhibitory effect was shown with aqueous extracts [21].

In another study of the same author, different organic extracts of eight plants were tested against AHH activity and ^{3}H-BP binding to DNA *in vitro*. The obtained *in vitro* effects of plants are similar with the *in vivo* effects from the previous study, and MC showed significant inhibitory effect when n-butanol extract was used. The n-butanol extract was more effective than the extracts of chloroform and petroleum-ether, respectively. None of the aqueous extracts showed any inhibitory effects on both AHH activity and ^{3}H-BP binding to DNA [22].

In a screening study performed at UNLV Cancer Research Institute at Brigham Young University, essential oils of various plants were tested against different cancer cell lines at 2005. At 100 μg/ml concentration, MC essential oil showed 81.4% cell line inhibition at breast cancer cell line, while at 200 μg/ml concentration the inhibition percent was 67 and 95.2 for prostate and breast cancer cell lines, respectively. Probably, the most exciting and hopeful result of this study is the inhibition value of essential oil of MC on 3T3 fibroblast cell line is 3.7% and 6.5% for the dosages of 100 μg/ml and 200 μg/ml, respectively. We may talk about a selective anticancer effect

Table 1: Summary of studies about anticancer properties of *Myrtus communis* L.

Key findings	Used part(s)	Reference
Ethanolic extract of MC inhibited AHH activity and ^{3}H-BP binding to rat liver microsomal protein	Ethanolic, water extracts	[21]
n-butanol extract of MC inhibited AHH activity and ^{3}H-BP binding to DNA *in vitro*	n-butanol, chloroform and petroleum-ether extracts	[22]
At 200 μg/ml concentration the inhibition percent was 67, 95.2 and 6.5 for prostate and breast cancer cell lines and 3T3 fibroblast cell line respectively	Essential oil	[23]
Authors tested of MC essential oil increased survival time on Ehrlich tumour of injected CD1 mice	Essential oil	[24]
MC water extract provides almost complete cure in Erlich ascites tumour injected mice	Water extract	[25]
Methanol and hot water extracts of MC were tested for their anticancer activities against two cancer cell lines (5637 and MCF-7): IC_{50} values for anticancer activity test was calculated as >50 μg/mL	Methanol and hot water extracts	[26]
Myrtucommulone-A induced apoptosis in cancer cell lines, with marginal cytotoxicity for non-transformed cells, via the mitochondrial cytochrome c/ Apaf-1/caspase-9	Myrtucommulone-A	[5]
Aromatic phloroglucinol core is essential for the cytotoxic activity of myrtucommulone	Myrtucommulone A, J, K, L	[12]

AHH: Aryl hydrocarbon hydroxylase, ^{3}H-BP: ^{3}H-benzo(a)pyrene, MC: *Myrtus communis*

amlording to these results. This kind of screening studies are fast, inexpensive, and very useful for providing well-directed leads for further studies [23].

In another study, authors tested MC for its anticancer effects on Ehrlich tumor of injected CD1 mice. In this study, authors postulated that MC distilled oil has cancer preventive properties, and they determined maximum tolerance dose (MTD) for MC distilled oil first. At the CD1 race mice, MTD is found 2 ml/kg and the LD50 is 2.5 ml/kg. From the four group of animals into which Ehrlich tumor is injected, one group is used as a control group, the other three groups are given different doses of MC L. (Doses are 0.1, 0.2, 0.4 ml/kg for the 2, 3, 4, experiment groups, respectively). Survival time increased in the experiment groups significantly [24].

Furthermore, we performed a similar study with Erlich ascites tumor injected mice and found that MC water extract provides almost complete cure in these animals when injections for extract and ascites cells had been started to apply together. In our study, animals with Erlich ascites tumor died about 19 days after injection, but extract treated animals continue to live and we terminated the study at 29th day of the experiment and showed that there is also histopathologically sumlessful cure [25].

Methanol and hot water extracts of MC were tested for their anticancer activities against two cancer cell lines (5637 and MCF-7) by Yemeni researchers. Authors also tested plant extracts for their antimicrobial and antioxidant activities. Although antimicrobial activity with MIC values ≤125 μg/mL against Gram-positive bacteria and a significant antioxidant activity were determined for MC, IC_{50} values for anticancer activity test were calculated as >50 μg/mL [26].

Myrtucommulone, a nonprenylated acylphloroglucinol, is probably one of the most attracting molecules in MC. Besides its other properties, recently it was shown that myrtucommulone-A induced apoptosis in cancer cell lines, with marginal cytotoxicity for non-transformed cells, via the mitochondrial cytochrome c/Apaf-1/caspase-9 [5]. In the mentioned study, authors showed that cell death had been caused via apoptosis and they found it to be much less cytotoxic for non-transformed human peripheral blood mononuclear cells (PBMC) or foreskin fibroblasts (EC_{50} cell death = 20-50 μM), and myrtucommulone up to 30 μM hardly caused processing of poly(ADP-ribose)polymerase (PARP), caspase-3, -8, and -9 in human PBMC. They concluded that the myrtucommulone -induced apoptosis was mediated by the intrinsic rather than the extrinsic death pathway; hence, myrtucommulone caused loss of the mitochondrial membrane potential in MM6 cells and evoked release of cytochrome c from mitochondria. Furthermore, it was found that Jurkat cells deficient in caspase-9 were resistant to myrtucommulone-induced cell death and no processing of PARP or caspase-8 was evident. In cell lines deficient in either CD95 (Fas, APO-1) signaling, FADD or caspase-8, myrtucommulone was still able to potently induce cell death and PARP cleavage [5].

When different myrtucommulones were tested against different cancer cell lines, it was shown that aromatic phloroglucinol core is essential for the cytotoxic activity; myrtucommulone types without phloroglucinol core do not have cytotoxic effects against some cancer cell lines while myrtucommulones with phloroglucinol core have cytotoxic effects against the same cancer cell lines [12].

These results are so important and exciting, because all of these findings look like that sound of footsteps of the pioneer of an ideal and selective anti-cancer drug in the near future [27]. But we need to perform new studies in order to support and improve the results for developing long-awaited cancer drug.

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