

## Biological effects of four frequently used medicinal plants of Lamiaceae

### Minireview

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Cancer is one of the leading causes of death characterized by uncontrolled growth and spread of cancer cells. There are several hundred thousands of new cases of cancer worldwide. Clinical oncology is still challenged by toxicity and side effects of multimodal therapy strategies in which it is associated with poor prognosis for patients. There is an urgent necessity to develop novel therapy strategies and to utilize preventive potential of natural compounds. As the majority of anticancer drugs are of natural origin, natural products represent a valuable source for the identification and development of novel treatment options and chemopreventive mechanisms for cancer. This review is focused on the summary of published knowledges on the antioxidant and potential chemopreventive effects of biologically active substances present in the extracts of four plants of the family Lamiaceae (sage, thyme, rosemary and lavender) in different animal and *in vitro* systems. It is assumed that the chemopreventive and chemotherapeutic potential of natural compounds is the result of a combined action of several mechanisms.

*Key words: sage, thyme, rosemary, lavender*

Chemoprevention represents a promising strategy for cancer reduction. It is defined as a use of natural or synthetic substances to prevent cancer formation or cancer progression. The chemopreventive effects of natural compounds are based at least in part on the induction of defense system involving detoxification and antioxidant enzymes, on their anti-inflammatory activity, on the ability to interfere with the cell cycle and to induce apoptosis [1].

Many mechanisms of natural compounds action have been described in connection with anticancer activity. Great attention is devoted to intracellular signaling cascade as a target for natural compounds. Numerous plant derived compounds were evaluated as potent anti-tumorigenic agents in *in vivo* and *in vitro* systems. Multiple epidemiological studies and experimental carcinogenesis studies suggest a significant correlation between the consumption of foods rich in fruits and vegetables and the reduced occurrence of cancers [2].

Tumor formation is a multistage process involving series of events generally occurring over an extended period. During these processes, accumulation of genetic and epigenetic

alterations leads to the progressive transformation of a normal cell into a malignant cell [3]. The plant extracts due to their unique features act at different levels and influence many cellular processes. They are becoming increasingly the main subject of chemotherapy research. Many researches are focused on the development of alternative approaches exploiting the potential of plant extracts in order to minimize the radiation dose through selective sensitivity of tumor cells and thus reduce the harmful effects of treatment [4].

Positive effects of Lamiaceae plants are attributed to the biologically active compounds which could reduce severe impacts of the environment or life style and eliminate side effects of drugs (Table 1). Chemopreventive activities of *Salvia officinalis*, *Thymus vulgaris*, *Rosmarinus officinalis* and *Lavandula angustifolia* presented in this review are summarized in Table 2.

In addition, plant extracts have other advantages, they are easily available, cheap and relatively safe with fewer side effects than synthetic compounds used in chemotherapy [5]. Currently, some plant extracts are in the stage of clinical trials and others were approved for use.

**Table 1. Antioxidant capacity, total phenolic content, and comparison of rosmarinic acid content in species from Lamiaceae, Papaveraceae and Lauraceae.**

Scientific name and family	Common name	Country/ place	Edible parts tested	TEAC (nmol trolox/100 g of DW) <sup>a</sup>	Total phenolic content (g GAE/100 g of DW) <sup>b</sup>	Content of rosmarinic acid (mg/100 g of DW)
<i>Cinnamomum zeylanium</i> N. (Lauraceae)	cinnamon stick	Indonesia	cortex	107.69	11.90	-
<i>Origanum vulgare</i> L. (Lamiaceae)	oregano	New Zealand	leaf	100.67	10.17	2562.7
<i>Salvia officinalis</i> L. (Lamiaceae)	sage	New Zealand	leaf and branch	51.89	5.32	2186.1
<i>Thymus vulgaris</i> L. (Lamiaceae)	thyme	New Zealand	leaf and branch	38.07	4.52	681.1
<i>Rosmarinus officinalis</i> L. (Lamiaceae)	rosemary	New Zealand	leaf and branch	37.8	5.07	1286.4
<i>Mentha canadensis</i> L. (Lamiaceae)	mint	Hong Kong	leaf and branch	33.83	5.15	1908.5
<i>Ocimum basilicum</i> L. (Lamiaceae)	sweet basil	New Zealand	leaf	29.59	3.64	1086.1
<i>Papaver somniferum</i> L. (Papaveraceae)	poppy	Dutch	seed	0.55	0.04	-

<sup>a</sup>TEAC, trolox equivalent antioxidant capacity. Data expressed as mmol of trolox equivalent/100 g of dry weight (DW). <sup>b</sup>Total phenolic content expressed as g of gallic acid equivalent (GAE)/100 g of dry weight (DW). (taken from Shan et al. [14])

**Salvia officinalis.** *Salvia officinalis* L. (common sage or garden sage) is a well-known medicinal plant used for centuries as a remedy for many diseases and as a cuisine matter. This plant of the family Lamiaceae, native to the Mediterranean region, is known for its antibacterial, anti-inflammatory, antifungal, antioxidant and antiproliferative activities [6-9].

The bioactive components present in sage are terpenoids and phenolic compounds, the two major secondary metabolites of *S. officinalis*, that could be responsible for the pharmacological effects of this plant [8]. Among terpenoids, volatile oils have been largely investigated because of their broad range of applications in food, cosmetic and pharmaceutical industry [10]. Sage essential oil (EO) is a mixture of volatile compounds, predominantly of low molecular weight terpenes, containing more than 50 compounds, being  $\alpha$ -thujone,  $\alpha$ -humulene, 1,8-cineole, caryophyllene, camphor and borneol as the major constituents. The EO composition is highly influenced by genetic and environmental factors, climate conditions, season, and culture site [10, 11].

Sage contains also important bioactive terpenoids such as triterpenoid ursolic and oleanolic acids [12] characterized by high lipophilicity [13]. Both components manifested hepatoprotective, anti-inflammatory, antihyperlipidemic and antitumorogenic properties [13].

The majority of the phenolic compounds in *Salvia* species is almost exclusively rosmarinic acid with strong antioxidant activity. There is increasing evidence to suggest that the antioxidant activity of rosmarinic acid is due to the presence of two ortho-dihydroxy groups (catechol structures) [14]. Besides this phenolic acid, phenolic diterpenes such as carnosic acid and carnosol were found in sage and reported to possess strong

antioxidant activities. Additionally, many other polyphenolic sage constituents were identified that could contribute to its antioxidant properties including caffeic acid as well as luteolin-7-glucoside (Fig. 1) [15].

**Thymus vulgaris.** *Thymus vulgaris* L. is a perennial herb indigenous which grows in central and southern Europe, Africa and Asia. It is rich in essential oils and antioxidant phenolic substances [16]. TV is widely used in folk medicine for the treatment of a variety of diseases including gastroenteric and bronchopulmonary disorders and in anti-worm, antispasmodic, carminative, sedative and diaphoretic remedies [17].

Quantitatively, the most important compounds in thyme are thymol and carvacrol, isoforms of the same monoterpene, which represent almost three-quarters of total volatiles, followed by terpenes, linalool (4%),  $\alpha$ -terpineol (2,4%), 1,8-cineole (2,1%), and borneol (2%) [18]. As the main components of thyme, triterpenic acids [19] and phenolic compounds [20] were identified similarly as for sage.

Roby et al. [20] provided evidence that cinnamic acid was the dominant phenolic compound in thyme methanolic extract, since it constituted 28% of the total extracted compounds followed by the two principal flavonoids: apigenin (8%) and luteolin-7-o-rutinoside (7%). Protective effect of *T. vulgaris* essential oil against aflatoxin B1-induced toxicity in rats has been reported by El-Nekeety et al. [21]. Aflatoxin B1, a well-known hepatocarcinogen, disturbs lipid profile in serum, decreases total antioxidant capacity, increases creatinine, uric acid and nitric oxide in serum and lipid peroxidation in liver and kidney accompanied with changes in the liver tissues. The oil alone did not induce any significant changes in the biochemical parameters, while the combined treatment showed significant

**Table 2. Summary of chemopreventive effects induced by extracts of Lamiaceae plants and their main constituents/components**

Plant species	Cells/animal models	Constituents	Chemopreventive effects	Refs	
Sage	-	Sage extract	Shown substantial antioxidant activity compared with BHT	[18]	
	Brain, liver homogenate <i>in vitro</i>		Inhibited lipid peroxidation and manifested high reducing power	[23,25]	
	Human hepatoma HepG2 cells		Prevented lipid peroxidation and GSH depletion	[25]	
	Different human colon cell lines		Protected DNA against oxidative and alkylating agents and stimulated DNA repair	[27,28,29]	
	Human colon carcinoma HCT15, CO115 cells		Induced apoptosis and inhibited MAPK/ERK phosphorylation	[9]	
	Human colon carcinoma HCT116 cells		Suppressed NFκB activation and degradation of IKK	[32]	
	Human endothelial cells		Inhibited angiogenesis due to anti-migratory effect	[36]	
Thyme	-	Thymol	Exhibited the strongest antioxidant capacity of thyme volatile extract	[40]	
	Liver, kidney in rat	Thyme extract	Protected cells against aflatoxin B1-induced toxicity	[43]	
	Hamster lung V79 cells, human hepatoma HepG2 cells	Thymol	Shown free radical scavenging activity, reduced lipid peroxidation and effected activity of enzymatic antioxidant defense system	[45,46]	
	Acute promyelotic leukemia HL-60 cells		Induced cell cycle arrest in G0/G1 phase, pro-apoptotic signaling pathway and apoptosis	[44]	
	Different human cell lines	Carvacrol	Defended oxidative DNA damage induced by H <sub>2</sub> O <sub>2</sub>	[49,50]	
	Breast cancer cells	Thyme extract	Caused cytotoxicity and apoptosis in cancer cells but not in normal cells	[59]	
	Human hepatoma HepG2 cells	Carvacrol	Induced apoptosis by activation of caspase-3 and altered MAPK cell signalling	[60]	
Rosemary	Human colon carcinoma Caco-2 cells, V79, HepG2 cells	Rosemary extract	Shown DNA-protective effects against oxidative damage	[70,72,73]	
	Human hepatoma HepG2 cells		Modulated activity of antioxidant, detoxifying and repair enzymes	[70,71]	
	Skin and liver cells (DMBA-treated mice)		Decreased lipid peroxidation, increased activity of SOD, CAT and GPx	[69]	
	Mouse macrophages/monocytes, colon cancer HT-29 cells		Reduced NO production, COX-2 expression and AP-1 activation	[77,78]	
	Neuronal HT22 cells		Carnosic acid	Induced cell cycle arrest and Nrf2 pathway activation	[81]
	Human hepatoma HepG2 cells, human leukemia cells		Carnosol	Caused G2/M cell cycle arrest and apoptosis through down-regulation of Bcl-2	[83,85]
Lavander	-	Lavander extract	Possessed less antioxidant activity than other members of Lamiaceae family, scavanged ROS	[18,94]	
	-		Inhibited both enzyme-dependent and enzyme-independent lipid peroxidation	[97]	
			Increased activity of SOD, CAT and GPx	[105]	
	Mouse macrophages/monocytes		Linalool	Decreased production of proinflammatory cytokines	[88]
	Human leukemia cells		Linalool	Induced activation of p53, cyclin-dependent kinase inhibitors and apoptosis without affecting growth of normal hematopoietic cells	[110]

improvements in all tested parameters and histological pictures in the liver tissues.

Antispasmodic, antibacterial and anti-inflammatory activity of thymol has been reported by Deb et al. [22]. Previous investigations on thymol have indicated its cytoprotective activity against radiation-induced damage in *in vitro* and *in vivo* model systems.

Carvacrol and thymol showed antigenotoxic properties against known mutagens [23] and they also exhibited protective effects against H<sub>2</sub>O<sub>2</sub>-induced DNA damage in human

colonic Caco-2, hepatoma HepG2 and leukemic K562 cell lines [24-25].

**Rosmarinus officinalis.** *Rosmarinus officinalis* L., commonly referred as rosemary, is an evergreen branched and bushy shrub of Mediterranean origin and it has become a common household plant in many parts of the world. Rosemary is also used in medicine and cosmetics. In folk medicine it is used as an analgesic, anti-rheumatic, diuretic agent, expectorant and as hepatoprotectant [26]. Rosemary crude extract showed a number of *in vitro* and *in vivo*

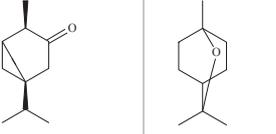
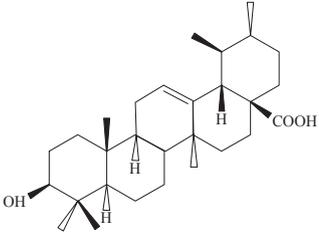
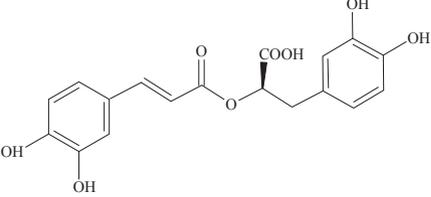
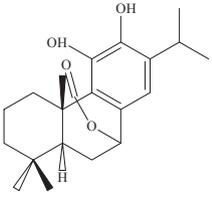
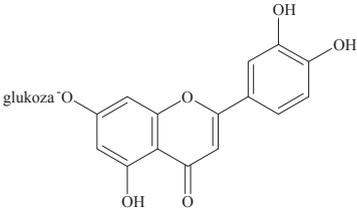
a. monoterpenes	b. triterpenic acid	c. phenolic acid
 <p><math>\alpha</math>-thujone</p> <p>1,8-cineole</p>	 <p>ursolic acid</p>	 <p>rosmarinic acid</p>
d. phenolic diterpene	e. flavonoid	
 <p>carnosol</p>	 <p>luteolin-7-glucoside</p>	

Figure 1. Chemical structures of main compounds in species from Lamiaceae.

biological activities including strong antioxidant power, antimutagenic effects [27], anti-inflammatory activities and *in vitro* anti-metastatic properties in B16/F10 mouse melanoma cells [28].

Some of the protective effects of rosemary extracts were attributed to enhancement of xenobiotic detoxification [29]. Two main compounds of rosemary, carnosol and carnosic acid inhibited mRNA expression and activity of cytochrome P450 (CYP1A) and increased glutathione S-transferase (GST) and quinon reductase mRNA expression and activities in human liver and bronchial cells [30, 31]. Administration of rosemary extract to rats resulted in significantly higher activities of phase II enzymes: GST and NAD(P)H quinone reductase in their livers and the authors proposed that carnosol may have an important role in the antitumour activity of rosemary extracts [31].

It is interesting to note that constituents in rosemary have shown a variety of pharmacological activities including anti-inflammatory properties. Cheung and Tai [32] provided that rosemary significantly reduced nitric oxide (NO) production by lipopolysaccharide (LPS)-activated cells in a dose-dependent manner. Moreover, rosemary extract suppressed interleukin-1 $\beta$  and cyclooxygenase-2 (COX-2) mRNA expression in these cells when compared to the untreated control. Scheckel et al. [33] proved that rosemary extract antagonizes

activator protein-1-dependent activation of COX-2 expression in human cancer and nonmalignant cell lines. Based on literature data, carnosol, the phenolic diterpene found in rosemary, has potential to inhibit LPS-induced activation of two members of the mitogen-activated protein kinases, specifically extracellular signal-regulated kinase (ERK) and p38, and abrogated LPS-induced iNOS expression [34]. Study of Kontogianni et al. [35] indicated immunomodifying activity of rosemary extract attributed to the presence of betulinic acid and higher concentration of carnosic acid in comparison to *S. officinalis*. Moreover, both extracts exerted cytotoxic activity through dose-dependent impairment of viability and mitochondrial activity of rat insulinoma m5F (RINm5F) cells. Decrease of RINm5F viability was mediated by NO-induced apoptosis [35].

**Lavandula angustifolia.** *Lavandula angustifolia* (true lavender or English lavender) is a well-known aromatic plant rich in volatile oil which is frequently reported to contain linalool (20-50% of the fraction) and linalyl acetate (25-46% of the fraction) as the major oil constituents [36]. The plant was also reported to contain phenolics including flavonoids and the caffeic acid derivative of rosmarinic acid [37]. However, elaboration of our literature survey revealed that there is still a lack of detailed data on the polyphenolic contents as well as on the pharmacological activities of *L. angustifolia*.

Majority of results concerning the effects of lavender in different model systems was obtained with lavender oil or with some of the major components of *L. angustifolia*. Lavender essential oil, volatile aromatic oily liquids isolated from Lavandula plants, possesses many therapeutic properties including antioxidant [38], anti-inflammatory [39], antimicrobial [38, 40], antiplatelet and antithrombotic [41], antimutagenic [42] and chemopreventive [40, 43] activities.

The study of Hudaib et al. [44] reported for the first time the xanthine oxidase (XO) inhibitory activities of *L. angustifolia*. Xanthine oxidase serves as an important biological source of oxygen-derived free radicals that contribute to the oxidative damage of living tissues. The authors provided that lavender is a good source of effective crude inhibitors for XO which can be used in the treatment of gout and other XO-related disorders. An Eastern European study on rats reported that inhalation of the lavender essential oil may be able to restore normal activity of oxidative enzymes involved in normal metabolism [45].

A Japanese study reported that lavender oil inhibited the generation of singlet oxygen which causes the most damage in response to UVA/UVB radiation [46]. This suggests that the regular use of lavender oil in skin preparations could suppress the aging effects of sunlight on the skin. Wang et al. [47] found that treatment with lavender oil significantly decreased neurological deficit scores, infarct size, the levels of malondialdehyde, carbonyl and reactive oxygen species (ROS), and attenuated neuronal damage, upregulated antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) activities. These results suggested that the neuroprotective effects of lavender oil against cerebral ischemia/reperfusion injury in mice may be attributed to its antioxidant effects [47].

Until now, most studies indicated that anti-mutagenic properties may be due to inactivation of the mutagens by direct scavenging, antioxidant capture of radicals produced by a mutagen or activation of cell antioxidant enzymes [11]. Lavender oil also showed moderate antimutagenicity against *Salmonella typhimurium* TA98 strain exposed to the direct mutagen 1-nitropyrene [40]. Lavender main components, linalool and linalyl acetate, showed no mutagenic potential in Ames mutagenicity test, with or without metabolic activation [48], and linalool did not induce chromosomal aberrations when incubated with Chinese hamster ovary cells [49]. Besides, Huo et al. [39] investigated protective effects of linalool on inflammation in LPS-stimulated RAW 264.7 cells and in LPS-induced *in vivo* lung injury model. They demonstrated that linalool significantly decreased LPS-induced production of proinflammatory cytokines (tumor necrosis factor- $\alpha$  and interleukin-6) *in vitro* and *in vivo*. Furthermore, the activation of the nuclear factor- $\kappa$ B (NF- $\kappa$ B) and MAPK pathways was blocked by linalool *in vitro*.

**Antioxidant effects of the compounds studied.** Flavonoids and many other phenolic compounds of plant origin have been reported as ROS scavengers and are viewed as promising therapeutic drugs for free radical pathologies. Many plants

belonging to Lamiaceae family show strong antioxidant activity and are considered to be useful agents for the prevention of different diseases.

**Antioxidant activity of *S. officinalis*.** Antioxidant activity of sage leaf extracts is largely attributable to various phenolic constituents including phenolic diterpenes such as carnosol [50] and hydroxycinnamic acid derivatives, notably rosmarinic acid [51]. In  $\beta$ -carotene bleaching test, the antioxidative activity of a dry acetone extract (15:1) from sage leaf was found to be 101-116% of that of the synthetic antioxidant butylated hydroxytoluene (BHT) [52]. Miliauskas et al. [37] described the relationship between phenolic content in sage and its ability to scavenge free radicals. Scavenging of intracellular ROS is one of the potential mechanisms contributing to the protective effects of many antioxidants [53].

Phospholipids of cellular membranes are extremely susceptible to oxidation due to their high content of polyunsaturated fatty acids, which participate in free radical chain reactions. Initial products, such as lipid hydroperoxides, afterwards produce reactive aldehydes and epoxides in the presence of metals [54]. The most prominent one is malondialdehyde, which is not only mutagenic and carcinogenic in mammals [55] but it can further react with DNA bases to form deleterious adducts. Protective effect of *S. officinalis* leaf on lipid peroxidation induced by some pro-oxidants was proved in rat brain and liver homogenates *in vitro*, and the effect of aqueous extract was attributed to the high reducing power and Fe(II) chelating ability which was accompanied with low hydroxyl radical scavenging ability [56]. Zupko et al. [57] reported that lipid peroxidation in both enzyme-dependent and enzyme-independent test systems were inhibited more effectively by sage leaf extract than by  $\alpha$ -tocopheryl acid succinate (used as a positive control) and the antioxidant activity was attributed mainly to rosmarinic acid.

Oxidative DNA damage is present in relatively small amount in cells due to the balance between DNA damage and its repair. Plant extracts rich in phenolic compounds inhibited DNA breaks and 8-oxoguanine lesions induced by oxidative agents [58]. Ramos et al. [58] demonstrated chemopreventive effects of *S. officinalis* and *S. fruticosa*, and the isolated compounds (rosmarinic acid and luteolin-7-glucoside) by protecting cells against oxidative agents and stimulating DNA repair, (*S. officinalis*, *S. fruticosa* and luteolin-7-glucoside) in Caco-2 and HeLa cells. These authors showed that sage extract tested and rosmarinic acid, its main constituent, protected human colon cell line CO115 from DNA damage induced by 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU). Sage water extracts and rosmarinic acid did not markedly change DNA repair protein expression in either cell line. Data showed that sage tea protected human colon cells against oxidative and alkylating DNA damage and may also interfere with efficacy of alkylating agents used in cancer therapy [59]. The study of Silva et al. [60] provided evidence that rosmarinic acid increased the repair of oxidized bases induced with the photosensitizer compound (Ro 19-8022) and had an effect on the expression

of OGG1 repair gene in PC12 neuronal cells. Garrera et al. [61] showed that a flavonoid-rich diet increases expression of some DNA repair genes such as XRCC3 (involved in double strand breaks repair) in healthy male smokers.

**Antioxidant activity of *T. vulgaris*.** Thymol, the main constituent of thyme, was found to be also a main contributor to the antioxidant activity of thyme volatile extract at 10 µg/ml, comparable to those of known antioxidants, BHT and  $\alpha$ -tocopherol at the same concentrations. Besides these, essential oil of thyme showed moderate inhibition of LDL oxidation and during autoxidation of lipids thymol was more effective in preventing oxidation than carvacrol [18].

Many studies provided evidence that monoterpenes thymol and carvacrol, the main components present in essential oil of thyme, possess antioxidant capacity. Thymol was found to inhibit various free radicals generated *in vitro*, including hydroxyl radicals, which would be considered as the primary reactive species responsible for the radiation-induced damage of bio-macromolecules, including DNA. In addition, thymol inhibited the radiation-induced decrease in intracellular glutathione, SOD and CAT enzyme levels in V79 cells accompanied by the reduction in lipid peroxides [62]. Same results indicated Phi et al. [63] who demonstrated protective effect of thymol against lipid peroxidation using HepG2 cells, radical-scavenging capacity as well as reducing power. Thus, Aeschbach et al. [64] reported that thymol and carvacrol possessed useful antioxidant properties, decreased peroxidation of phospholipid liposomes in the presence of Fe(III) and ascorbate, and were good scavengers of peroxy radicals ( $\text{CCl}_3\text{O}_2^{\cdot}$ ) but did not accelerate DNA damage in the bleomycin-Fe(III) system. Damage to DNA in the presence of a bleomycin-Fe complex has been accepted as one of the mechanism for examination of the potential pro-oxidant actions of lipid antioxidants.

**Antioxidant activity of *R. officinalis*.** The most important chemical constituents of rosemary include flavonoids such as carnosol, carnosic and rosmarinic acids and volatile oils [65]. Carnosol and carnosic acid constitute 3.8–4.6% and 0.1–0.5%, respectively [66]. Carnosic acid is not stable during processing and storage. It is first oxidized to carnosol which undergoes further oxidative transformation to form rosmanol [67]. Moreover, carnosic acid and carnosol are considered to account for more than 90% of the antioxidant properties of the rosemary extract; they are powerful inhibitors of lipid peroxidation and good scavengers of peroxy radicals [68]. Studies on the chemical composition of *R. officinalis* confirmed also the presence of monoterpenes including  $\alpha$ - and  $\beta$ -pinenes, together with 1,8-cineole, borneol and camphor (20–50% of the oil) [69, 70]. Zegura et al. [69] studied antioxidant and antigenotoxic effects of rosemary extract against mutagens 4-nitroquinoline-N-oxide and 2-amino-3-methyl-3H-imidazo[4,5-F]quinoline using *Salmonella typhimurium*. Additionally, they provided evidence that *R. officinalis* protects HepG2 cells in pre- and co-treatment with *tert*-butyl hydroperoxide (*t*-BHP). In co-treatment procedure, when HepG2 cells were simultaneously

exposed to rosemary extract and *t*-BHP, extract may protect cells against oxidant-induced DNA damage directly either by free radical scavenging activity or by decreasing free radical production through iron chelation [71]. On the other hand, in the case of pre-treatment, extract may indirectly act as antioxidant in cells by modulating the activity of antioxidant, detoxifying and repair enzymes as well as enzymes involved in the bioactivation of xenobiotics [72]. This is in agreement with findings of Slamenova et al. [73] who described that pre-treatment of human colon cancer (Caco-2) and hamster lung (V79) cells with rosemary extract reduced the level of DNA strand breaks and oxidative DNA damage induced by  $\text{H}_2\text{O}_2$  and visible light-excited methylene blue. Recently, Horvathova et al. [74] showed that in hepatocytes isolated from rats supplemented with rosemary oil, decreased level of DNA damage induced by oxidative stress was detected in comparison to control rats.

**Antioxidant activity of *L. angustifolia*.** Lavender oil has shown a modest antioxidant activity in several assays [75]. Its antioxidant activity is less potent than in other members of the Labiatae family. In the study by Dapkevicius et al. [52], none of six different types of extracts from *L. angustifolia* exhibited any antioxidant activity in a  $\beta$ -carotene bleaching test. Other studies reported that lavender does exhibit antioxidant properties. In the study by Billany et al. [76] lavender oil and two of its chemical constituents, cineole and  $\beta$ -pinene, slowed the normal rate of a hydroxyl radical mediated chemical reaction more than either ethanol and mannitol, known hydroxyl radical scavengers. The essential oil of *L. angustifolia* mildly slowed auto-oxidation in lard [77]. Similarly, a phenolic compound from *L. angustifolia* prevented the development of oxidative rancidity in vegetable oils in a dose dependent manner comparable to 200 ppm butylated hydroxyanisole (BHA) and BHT [78]. Extracts of *L. angustifolia* exerted a concentration-dependent inhibition against both enzyme-dependent and enzyme-independent lipid peroxidation [79]. Blazekovic et al. [80] obtained correlation coefficients which exhibited a strong positive association among different modes of antioxidant action (antiradical activity, reducing power and inhibition of lipid peroxidation) and contents of phenolic acids and total polyphenols in lavender extracts, indicating that phenolic compounds could be the major contributors to their antioxidant properties.

**Chemopreventive effects of the compounds studied.** A large number of medicinal herbs were reported to have chemopreventive properties. It is important to note that chemopreventive agents may act by a different ways, as chemical inactivators, antimutagens, enzymatic inducers, antioxidants and tumor growth suppressors [81]. The can influence one of several steps of carcinogenesis (Figure 2). Many of nutritional substances might influence carcinogenesis through more than one mechanism. The most useful cancer chemoprotective agents should have significant ability to reduce tumor incidence, delay tumor onset and prevent tumor progression.

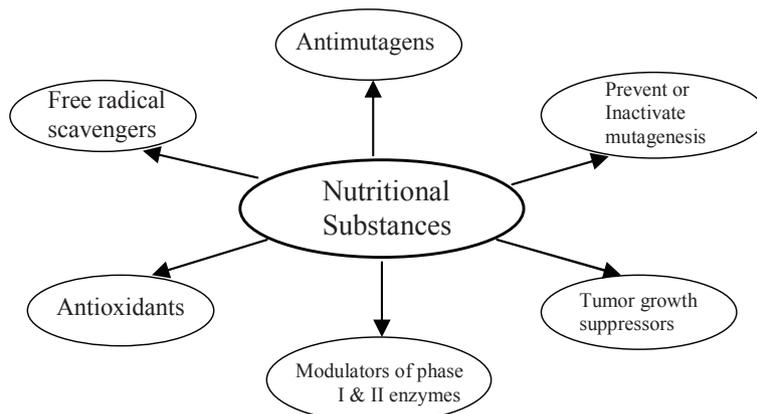


Figure 2. Possible roles of nutritional substances against carcinogenesis (taken from Manoharan et al. [81]).

**Chemopreventive effects of *S. officinalis*.** Inhibition of cell proliferation and induction of apoptosis represent the two strategies of chemopreventive agents to block tumor promotion. Aromatic plants of the genus *Salvia* (sage) except antioxidant activity have also been suggested to have anticancer properties based on antiproliferative activity on tumor cells [82]. In addition, ROS have been reported to play a role in signalling transduction enhancing proliferation and survival of cancer cells. Antioxidant phytochemicals, through their ROS scavenging activity, may suppress altered redox-sensitive signalling events in cancer. Xavier et al. [9] investigated the antiproliferative and proapoptotic effects of *S. officinalis*, *S. fruticosa* and rosmarinic acid on human colon carcinoma cell lines, HCT15 and CO115, which have different mutations in MAPK/ERK and phosphatidylinositol 3-kinase (PI3K/Akt) signalling pathways. Interestingly, they found that SF, SO and rosmarinic acid induce apoptosis in both cell lines, whereas cell proliferation was inhibited by the two sage extracts only in HCT15. SO, SF and rosmarinic acid inhibited ERK phosphorylation in HCT15 and had no effects on Akt phosphorylation in CO115 cells. The activity of sage extracts seems to be due, at least in part, to the inhibition of MAPK/ERK pathway. Moreover, the sage components linalyl acetate (Ly) and  $\alpha$ -terpineol (Te) exhibited synergistic antiproliferative effects. Deeb et al. [83] investigated the effect of Ly and Te on NF $\kappa$ B signaling in HCT-116 colon cancer cells. The combination of these components reduced dose-dependently cell viability at non-cytotoxic concentrations, increased cells at PreG1 phase and suppressed NF $\kappa$ B activation. Authors referred that NF $\kappa$ B suppression correlated with the inhibition of p65 nuclear translocation and I $\kappa$ B $\alpha$ -alpha degradation. Furthermore, separate treatments and drug combinations significantly decreased DNA binding activity of NF $\kappa$ B which led to the potentiation of cell death induced by the colon cancer drugs oxaliplatin and 5-fluorouracil. These study demonstrated possible use of Ly and Te in combination with chemotherapeutic agents to induce apoptosis and their

anticancer effects are partly mediated through the suppression of NF $\kappa$ B [83].

As mentioned before, sage is also known to affect signaling pathways. Sertel et al. [84] found that the three most significantly regulated pathways by sage were aryl hydrocarbon receptor signaling, cell cycle (G1/S checkpoint) regulation, and p53 signaling in cavity squamous human cell carcinoma cell line (UMSCC1).

Bauer et al. [85] demonstrated that carnosol and carnosic acid from *S. officinalis* suppressed the formation of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), the most relevant eicosanoid promoting inflammation and tumorigenesis. During biosynthesis of PGE<sub>2</sub>, arachidonic acid is transformed to prostaglandin H<sub>2</sub> (PGH<sub>2</sub>) by cyclooxygenases and further converted to PGE<sub>2</sub> by PGE<sub>2</sub> synthases [86]. Carnosol and carnosic acid inhibited PGE<sub>2</sub> formation by selectively targeting microsomal PGE<sub>2</sub> synthase (mPGES)-1, isoenzyme functionally coupled with COX-2. Both of these enzymes are induced by pro-inflammatory stimuli and overexpressed in tumors [85].

Over the last years, more attention is focused on the anti-angiogenic and anti-tumor effects of non toxic compounds present in commonly used herbs. Ethanol extract of *S. officinalis* exhibited a significant inhibitory activity on the endothelial cells migration as well as on the proliferation of different blood cells, but cell proliferation was suppressed only at higher concentration. These findings indicated that anti-angiogenic effect of sage extract might be due to anti-migratory activity [87] attributed to anti-proteases and/or interference of cytoskeleton organization which is known to play important roles in cell locomotion and capillary tube formation [88].

In an attempt to explain the cytoprotective activities, the effects of sage extracts and phenolic compounds on three markers of cellular oxidative stress (lipid peroxidation, glutathione [GSH] level and DNA damage) were evaluated. Both sage extract and phenolic compounds (rosmarinic acid and luteolin-7-glucoside) significantly prevented lipid peroxidation and GSH depletion but failed to prevent DNA damage induced

by *t*-BHP [89]. GSH plays an important role in hepatocyte defence against ROS, free radicals and electrophilic metabolites and its depletion may lead to alterations in cellular calcium homeostasis and subsequently to cell death [90]. Since the increase in GSH level was accompanied by an increase in total glutathione level (and not to a reduction in oxidized glutathione [GSSG] level), sage extracts seem to have an ability to increase *de novo* synthesis of glutathione [89].

DNA damage induced by oxidative and alkylating agents contributes to carcinogenesis, leading to possible mutations if replication proceeds without proper repair. However, some alkylating agents are used in cancer therapy due to their ability to induce DNA damage and subsequently apoptosis of tumor cells. Ramos et al. [27] found protective effect of *S. officinalis* extract against oxidative ( $H_2O_2$ ) DNA damage in human colon HCT15 cells and decreased DNA damage induced by N-methyl-N-nitrosourea in CO115 human colon cell line. In addition to chemopreventive effects of sage extracts, it was also important to know whether these plant extracts may interfere with alkylating agents such as nitrosourea used in cancer therapy, decreasing their efficacy.

**Chemopreventive activity of *T. vulgaris*.** Bozkurt et al. [91] reported that methanolic extract of *T. serpyllum* (wilde thyme) induced significant cytotoxicity and apoptosis in breast cancer cells but not in normal cells. It is notable that the extracts from thyme exhibited the strongest antioxidant capacity followed by sage and marjoram. As observed, extracts with higher antioxidant capacity had also higher polyphenol contents. Additionally, carvacrol inhibited 7,12-dimethylbenz(a)anthracene (DMBA) induced tumorigenesis in rats [92], growth of murine B16 melanomas [93] and human non-small lung cancer A549 cell line [94], while thymol significantly increased activities of antioxidant enzymes such as SOD and GPx in rats [95].

Induction of apoptosis and influence on the cell cycle as well as suppression of angiogenesis are playing roles in chemopreventive potential of many natural compounds. Apoptosis is an active form of cell suicide, leads to cell shrinkage, chromatin condensation, membrane blebbing and DNA degradation [96]. It is noteworthy that mitochondria play a vital role in induction of apoptosis through release of proteins that propagate both caspase-dependent and caspase-independent pathways. Deb et al. [22] reported on the anticancer activity of thymol on acute promyelotic leukemia HL-60 cells but did not show any cytotoxic effect in peripheral blood mononuclear cells. The cytotoxic effect of thymol on HL-60 cells appears to be associated with induction of cell cycle arrest at sub G0/G1 phase which is irreversible and leads the cell to undergo apoptosis. Thymol also showed significant increase in production of ROS activity, increase in mitochondrial  $H_2O_2$  production and depolarization of mitochondrial membrane potential. Some other important players in apoptosis were affected, there was observed increase in pro-apoptotic protein Bax level with a concomitant decrease in Bcl2 protein expression, one of the anti-apoptotic protein overexpressed in a wide variety of cancers [97].

Literatures have shown that loss of mitochondrial membrane potential leads to activation of caspases, which plays an important role in the execution phase of apoptosis. Initiator caspase, such as caspase-8 and caspase-9, either directly or indirectly activates effector caspases, such as caspase-3 [98]. Treatment of cells with thymol resulted in activation of initiator caspase-8 and -9, effector caspase-3 and then intracellular substrate, poly(ADP-ribose)polymerase (PARP) cleavage, resulting in apoptosis. Moreover, thymol was also able to induce caspase-independent apoptosis [22]. Research of Ferraz et al. [99] showed cytotoxicity of *Lippia gracilis* EO treatment on HepG2 cells. *Lippia gracilis* is a medicinal plant, which has thymol as its major constituent. In this study EO-treatment caused G1 arrest accompanied by the induction of DNA fragmentation without affecting cell membrane integrity. Cell morphology consistent with apoptosis and a remarkable activation of caspase-3 were also observed, suggesting induction of caspase-dependent apoptotic cell death. Carvacrol, one of the members of monoterpene phenols present in the volatile oils of *T. vulgaris*, inhibited viability and proliferation of A549 cells, a human non-small cell lung cancer, and induced early apoptotic features in a dose-dependent manner [94]. In the study conducted by Yin et al. [100], carvacrol affected apoptosis of human hepatoma HepG2 cells by the activation of caspase-3, cleavage of PARP and decreased Bcl-2 gene expression. Moreover, carvacrol selectively altered the phosphorylation state of members of the MAPK superfamily, decreasing phosphorylation of ERK significantly in a dose-dependent manner, and activated phosphorylation of p38 but not affecting JNK MAPK phosphorylation.

In animal model, Ferraz et al. [99] confirmed that EO of *Lippia gracilis* possesses antitumor activity. Mice were subcutaneously transplanted with sarcoma 180 cells and treated by intraperitoneal route with EO for 7 days and they showed tumor growth inhibition rates of 38.5–41.9%.

**Chemopreventive activity of *R. officinalis*.** Recent studies described pharmacological effects of rosemary in chemoprevention as well as in cancer therapy. In order to explore the chemopreventive properties of rosemary extract, Parmar et al. [70] focused their research on the antitumor-promoting activity of *R. officinalis* on skin carcinogenesis induced by DMBA in mice. After administration of rosemary extract to mice significant decrease in lipid peroxidation, GSH and total protein levels in their skin and livers was observed. Skin and livers of *R. officinalis* treated animals showed significant enhancement in activities of antioxidant enzymes such as SOD and CAT. This findings indicated that *R. officinalis* could reduce chemically induced tumors. Carnosol, the oxidized form of carnosic acid, also induced G2/M cell cycle arrest through altering the levels of cyclin A and cyclin B1 [101], inhibited invasion in B16/F10 melanoma cells, possibly through inhibition of NF $\kappa$ B signaling pathway. Constitutively active NF $\kappa$ B has now been identified in tissues of most cancer patients, including prostate, breast, oral, pancreas and colon cancer [102]. Carnosol limited the translocation of NF $\kappa$ B subunits to the nucleus and reduced NF $\kappa$ B DNA binding activity in activated

macrophages due to the inhibitor of kappa B inactivation [34]. Both carnosol and rosemary extract increased apoptosis through down-regulating Bcl-2 in human leukemia [103] and human ovarian cancer cells *in vitro* [104], respectively.

**Chemopreventive activity of *L. angustifolia*.** It has been reported that linalool exhibits antiproliferative activity against certain solid tumor cells, such as melanoma, renal adenocarcinoma [105] and HepG2 cells [106]. Particularly, linalool induced apoptosis in human leukemia cells without affecting growth of normal hematopoietic cells [107] and it was an effective doxorubicin modulator [108].

Perillyl alcohol (POH) was found in lavender, as well [109]. It blocks cell division, induces apoptosis and, in some cases, induces differentiation. In rats who received a diet supplemented with POH for 52 weeks, the total incidence of adenocarcinomas in the colon was significantly reduced, and the tumors that did occur exhibited a significantly higher apoptotic index compared to the tumors examined from unsupplemented animals [110]. In a randomized trial in mice, those given POH injections prior to administration of a lung carcinogen and three times a week for 22 weeks afterward showed a 22% reduction in tumor incidence and a 58% reduction in tumor multiplicity [109]. Perillyl alcohol is in Phase I clinical trials for use as a chemoprotective and chemotherapeutic agent against advanced breast, ovarian and prostate cancers [111]. Linalool, one of the major constituents of lavender oil, has shown very good *in vitro* activity against human basal cell carcinoma [112] and a topically applied 10% dilution of linalool reduced skin tumor incidence in mice by 33% [113].

## Conclusion

Lamiaceae family species are considered important because of their use in folk medicine and in culinary and flavouring remedies throughout the world. Their interesting bioactivities are attributed mainly to essential oils, polyphenols and terpenes. Numerous studies have demonstrated that plant extracts exhibit many useful technological and biological properties, e.g. it is well known that plant extracts have potent antioxidant power and more recent studies showed their anticarcinogenic and anti-inflammatory activities. Based on these findings plant extracts and their components represent promising candidates for their use in pharmacological industry or a fertile ground for the development of novel anticancer drugs structurally derived from natural compounds which, of course, require further extensive scientific and clinical investigations.

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