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Review Article

Anticancer activity of essential oils and their chemical components - a review

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Abstract: Essential oils are widely used in pharmaceutical, sanitary, cosmetic, agriculture and food industries for their bactericidal, virucidal, fungicidal, antiparasitical and insecticidal properties. Their anticancer activity is well documented. Over a hundred essential oils from more than twenty plant families have been tested on more than twenty types of cancers in last past ten years. This review is focused on the activity of essential oils and their components on various types of cancers. For some of them the mechanisms involved in their anticancer activities have been carried out.

Keywords: Essential oils, anticancer activity, chemical composition

Introduction

Recognized since ancient times for their medicinal value, but often considered as a relic of medieval medical practice by representatives of modern medicine, essential oils (EOs) are currently receiving therapeutic interest fully renewed. Thus, during recent years, plant EOs have come more into the focus of phytomedicine [1, 2]. Their widespread use has raised the interest of scientists in basic research of EOs. Especially, anti-microbial and anti-oxidant activities as well as potential anti-cancer activity have been investigated in recent years [3, 4].

Cancer is the second largest single cause of death claiming over six million lives every year worldwide [5]. There has been a recent upsurge in the use of natural products to supersede current treatment in patients that develop multidrug resistance. Scientific studies of plants used in various types of ethnic medicine has led to the discovery of many valuable drugs, including taxol, camptothecin, vincristine and vinblastine [6, 7]. Many studies pointed out anticancer properties of other plants [8-11]. Over five hundred papers have been published on anticancer activity of EOs. The first publications on the anticancer activity of essential oils dated to 1960s. So far, the effects of EOs have been investigated on glioblastoma, melanoma, leukemia and oral cancers, as well as on bone, breast, cervix, colon, kidney, liver, lung, ovary, pancreas, prostate, and uterus cancers.

The aim of this review is to state the work carried out on the anticancer properties of EOs, their mode of action and the types of cancers targeted.

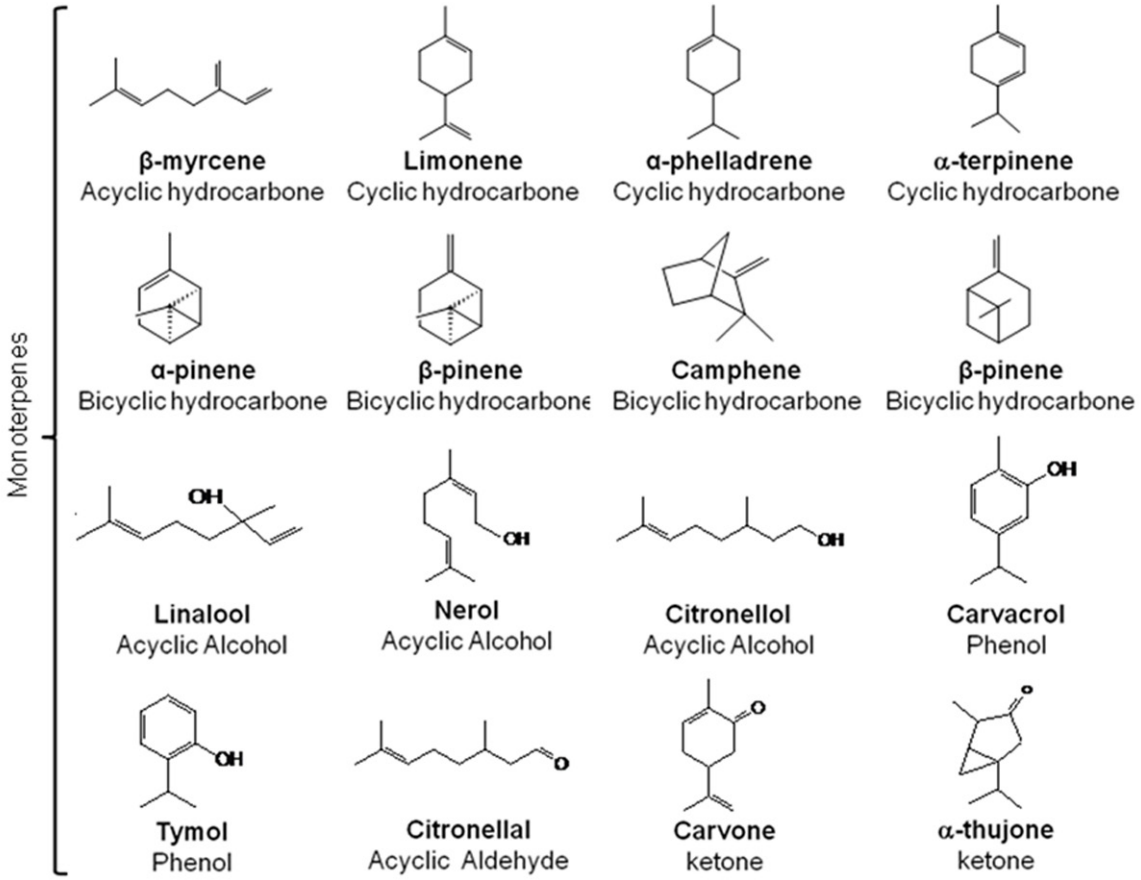

Figure 1. Examples of some monoterpenes compounds found in essential oils of plants.

Essential oils, a mix of complex molecules

EOs are natural, complexe, volatile, and odorous molecules synthesized by the secretory cells of aromatic plants [12]. Also known as volatile oils, EO could be considered as a generic term for the liquid and highly volatile components of plants, with a strong and characteristic odor. Altogether EOs are the concentration of hydrophobic liquid containing multiple volatile aroma compounds found in glands located in various parts of the aromatic plants: leaves, flowers, fruit, seeds, barks and roots.

Even though various methods could be used for their extraction, hydrodistillation remains the most used extraction method to obtain EOs, especially for commercial and medicinal purposes [13]. EOs can also be obtained by cold [14], liquid carbon dioxide at low temperature and high pressure, or ultrasound-assisted extraction or microwave [15]. Usually color less or pale yellow, EOs are volatile, flammable and odorous, and their density is generally less than 1 [16], except for cinnamon, cloves and sassafras. Insoluble in water and soluble in alcohols, oils and petrolatum, which explains the term "oil", they could be rapidly oxidized and isomerized by light [16].

Even though over 300 different compounds could be identified, three main groups of compounds have been described [17]. While the main group is composed of terpenes and terpenoids, the others include aromatic (phenolic) components, and in a lower extent aliphatic (alkanes and alkenes) compounds are generally in trace. All compounds are characterized by a low molecular weight [18].

Terpenes and terpenoids

About 30 000 terpenes have been described in the literature [19, 20]. Some of the most common have been represented in **Figures 1**, **2**. Their basic structure follows a general principle: 2-methylbutane, also refered as isoprene residues build up the carbon skeleton of terpenes $(C5)_n$, as described by Ruzicka [21]. They are subdivided according to the number of isoprene

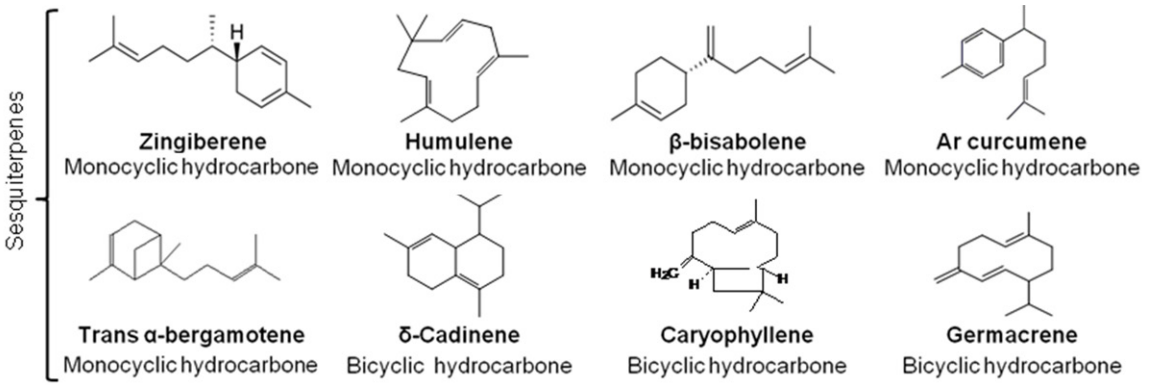

Figure 2. Examples of some sesquiterpenes compounds found in essential oils of plants.

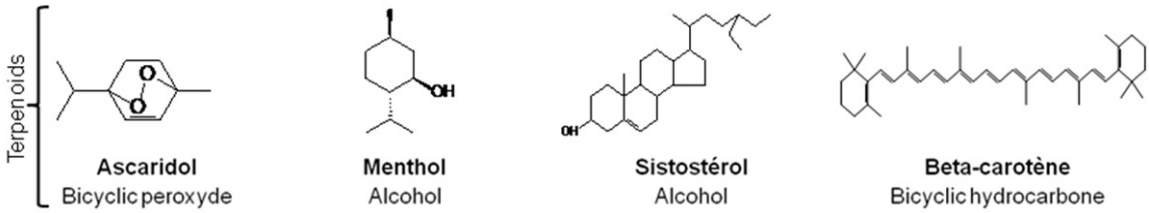

Figure 3. Examples of some terpenoids compounds found in essential oils of plants.

units in monoterpenes ($C_{10}H_{16}$), sesquiterpenes ($C_{15}H_{24}$), diterpenes ($C_{20}H_{32}$) and tetraterpenes, which contain eight units of isoprene such as carotenoids [22]. Terpenoids (**Figure 3**) are terpenes-derived compounds with one or more chemical functional groups (alcohol, aldehyde, ketone, acid...).

Aromatic compounds

Aromatic compounds (**Figure 4**) are phenyl propane derivatives. They are less abundant than terpenoids. Two classes of aromatic compounds can been distinguished: the nuclear substituted compounds and derivatives of benzene in which the substituent is directly attached to the benzene ring; the side chain substituted compounds.

Plant essential composition varies according to its environmental and living conditions

According to environmental and living conditions, the same species may show intraspecific chemical differences in its EO compositions [23, 24]. These intraspecific differences are defined as chemotypes.

Effects of EOs on various types of cancer

Most of EOs have been first identified and used for the treatment of inflammatory and oxidative diseases. It appeared that these EOs could also have anticancer effects as there is a relationship between the production of reactive oxygen species to the origin of oxidation and inflammation that can lead to cancer [25]. Initial experiments assumed that oxidative stress could act as a DNA-damaging agent, effectively increasing the mutation rate within cells and thus promoting oncogenic transformation. Besides, reactive oxygen species could also specifically activate signaling pathways and thus contribute to tumor development through the regulation of cellular proliferation, angiogenesis, and metastasis [26]. Hence chronic inflammation has been linked to various steps involved in carcinogenesis, such as cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis [27]. Several studies have thus shown that EOs and their components therein could be active against various cancer cells (**Table 1**).

Prostate cancer

EO of *Hypericum hircinum* L. subsp. *Majus* revealed antiproliferative activity on human prostatic adenocarcinoma (PC3) [28]. Jacaric acid and four of its octadecatrienoic geoisomers selectively induced apoptosis in hormone-dependent (LNCaP) and -independent (PC-3) human prostate cancer cells, whilst not

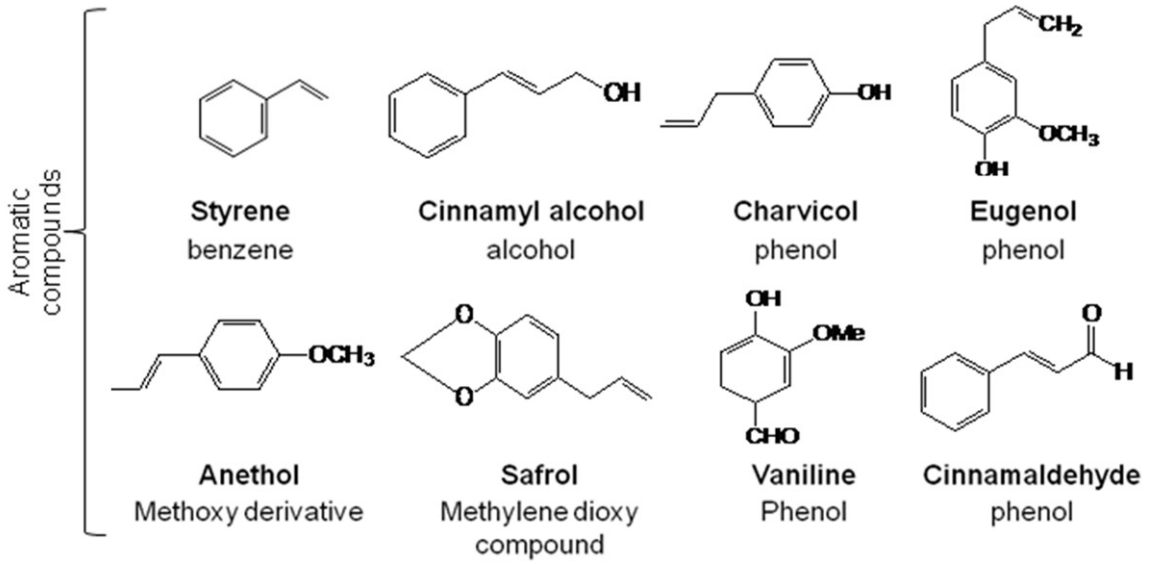

Figure 4. Examples of some aromatic compounds found in essential oils of plants.

affecting the viability of normal human prostate epithelial cells (RWPE-1) [29]. *Pinus wallichiana* EO showed significant anti-proliferative activity on prostate cancer cells [30]. *Solanum erianthum* leaf volatile oil demonstrated potent inhibitory activity against PC-3 cells [31]. *Thymus vulgaris* L. EO exhibited the strongest cytotoxicity towards three human cancer cells. Its half inhibitory concentration (IC_{50}) value on PC-3 tumor cell line was 0.010% (v/v) [32]. EO of *Mentha arvensis* showed cytotoxic activity on LNCaP cells [33]. Oxidative stress results from an imbalance in the production of reactive oxygen species (ROS) and cell own antioxidant defenses that in part leads to numerous carcinogenesis. Kim et al. [34] have shown that saponins contained in EO of ginger reduces the incidence of prostate cancer by exerting antimutagenic activity and also inhibits tumor metastasis. *Guatteria pogonopus* leaves showed significant *in vitro* and *in vivo* antitumor activity on PC-3M metastatic prostate carcinoma [35]. EOs from *Ageratum conyzoides* Linnæus and *Lippia multiflora* Moldenk were the most active on LNCaP and PC-3 cell lines [36].

Glioblastoma

EO of *Hypericum hircinum* had antiproliferative activity on human glioblastoma tumor cells T98G [28]. It increases cytosolic Ca^{2+} concentrations and alters the viability of human glioblastoma cells by inducing apoptosis [37]. *Zanthoxylum tinguassuiba* EO contains α-bisabolol, a known antiglioma sesquiterpene, among other potentially active substances [38]. It was observed that thermal-oxidative stability of the liposomal *Z. tinguassuiba* EO was enhanced when compared to its free form. The liposomal form also presented significant apoptotic-inducing activity for glioma cells. These results show that this EO could be a potential alternative for gliobastoma treatment [38]. The results of the studies whose the objective was to examine the augmentation of the therapeutic activity in human glioblastoma cells with combination of paclitaxel (PTX) and the apoptotic signaling molecule, C_6-ceramide (CER), show that PTX and CER can be used together to enhance therapeutic activity, especially in aggressive tumor models such as glioblastoma [39]. A recent study has showed that SF-767 glioblastoma cell line was the most sensitive to *Ocimum basilicum* Linnæus and *Lippia multiflora* Moldenk EOs, while essential oil of *Ageratum conyzoides* Linnæus showed the highest antitumoral activity on SF-763 cells [36].

Melanoma

EOs of *Afrostyrax lepidophyllus* and *Scorodophloeus zenkeri* exhibited a strong growth-inhibitory effect on human malignant melanoma A375 cell line [10]. The EO obtained from hydrodistillation of flowering aerial parts of *Athanasia brownii* also showed significant effect on A375 cells [40]. EOs from the leaves

Table 1. Summary of literature review (2004-2014)

Cancer	Essential oil or compound tested	Plant family	Cell line used	Reference
Brain	*Croton regelianus* and ascaridole compound	Euphorbiaceae	SF-295 (IC_{50} = 48.0 μg/ml and 8.4 μg/ml respectively)	[97]
Brain (glioblastoma)	*Afrostyrax lepidophyllus* and *Scorodophloeus zenkeri*	Huaceae and Caesalpiniaceae (Fabaceae)	T98G (IC_{50} = 15.4 μg/ml and 12.4 μg/ml respectively)	[10]
Brain (glioblastoma)	α-Bisabolol	---	T67 and C6: 50% of cell death after 24 h treatment with 2.5 μM	[94]
Brain (glioblastoma)	*Casearia sylvestris*	Salicaceae	U87 (IC_{50} = 27.1 μg/ml)	[42]
Brain (glioblastoma)	*O. basilicum, L. multiflora, A. conizoides, and Z. officiniale*	Lamiaceae, Verbenaceae, Asteraceae and Zingiberaceae respectively	SF-767 (0.30, 0.31, 0.43 and 0.48 mg/ml respectively) and SF-763 (0.43, 0.47, 0.38 and 0.44 respectively)	[36]
Brain (glioma)	*Malus domestica*	Rosaceae	C-6 (1 mg/ml = 58.5% inhibition)	[51]
Breast	*Afrostyrax lepidophyllus* and *Scorodophloeus zenkeri*	Huaceae and Caesalpiniaceae (Fabaceae)	MDA-MB 231 (IC_{50} = 10.9 μg/ml and 8.0 μg/ml, respectively)	[10]
Breast	*Satureja khuzistanica*	Lamiaceae	MCF7 (IC_{50} = 125 μg/ml)	[8]
Breast	*Casearia sylvestris*	Salicaceae	MCF-7 (IC_{50} = 42.2 μg/ml)	[42]
Breast	*Cedrelopsis grevei*	Rutaceae	MCF-7 (IC_{50} = 21.5 mg/L)	[43]
Breast	*Solanium spirale* Roxb.	Solanaceae	MCF-7 (IC_{50} = 19.69 μg/ml)	[44]
Breast	carbazole alkaloids	---	MCF-7 (IC_{50} = 2.12 μg/ml)	[98]
Breast	*Helichrysum gymnocephalum*	Asteraceae	MCF-7 (IC_{50} = 16 μg/ml)	[99]
Breast	*Pituranthos tortuosus* (Desf.)	Apiaceae	MCF-7 (IC_{50} = 3.38 μg/ml)	[54]
Breast	*Melaleuca armillaris*	Myrtaceae	MCF-7 (IC_{50} = 12 μg/ml)	[100]
Breast	*Rosmarinus officinalis*	Lamiaceae	MCF-7 (IC_{50} = 190.1 μg/ml)	[101]
Breast	*Schinus molle* L. and *Schinus terebinthifolius* Raddi	Anacardiaceae	MCF-7 (IC_{50} = 54 mg/ml and 47 mg/ml, respectively)	[102]
Breast	*Erigeron acris* L.	Asteraceae	MCF-7 (IC_{50} = 14.5 μg/ml)	[103]
Breast	*Aquilaria sinensis* (Lour.) Gilg.	Thymelaeaceae	MCF-7 (99.6% inhibition at 500 μg/ml)	[104]
Breast	*Thymus vulgaris* L.	Lamiaceae	MCF-7 (IC_{50} = 0.030% (v/v))	[32]
Breast	*Aristolochia mollissima* rhizome and the aerial part	Aristolochiaceae	MCF-7 (IC_{50} = 20.6 and 21.1 μg/ml respectively) and MDA-MB-435S (IC_{50} = 22.1 and 20.3 μg/ml respectively)	[59]
Breast	*Schefflera heptaphylla* (L.)	Araliaceae	MCF-7 (IC_{50} = 7.3 μg/ml)	[72]
Breast	β-caryophyllene oxide	---	MDA-MB-231	[78]
Breast (mouse)	*Angelica archangelica* fruits from separate locations A, B and C	Apiaceae	Crl (IC_{50} = 47.7; 91.8 and 63.6 μg/ml respectively)	[71]
Cervix	*Liquidambar styraciflua* leaf and stem	Hamamelidaceae	HeLa (IC_{50} = 136.27 and 119.78 μg/ml respectively)	[56]
Cervix	*Ocimum basilicum* Linn.	Lamiaceae	HeLa (IC_{50} = 90.5 μg/ml)	[105]
Cervix	carbazole alkaloids	---	HeLa (IC_{50} = 1.98 μg/ml)	[98]
Cervix	*Aristolochia mollissima* rhizome and the aerial part	Aristolochiaceae	HeLa (IC_{50} = 38.6 and 50.6 μg/ml respectively)	[59]
Ovary	D-Limonene	---	V79	[77]
Ovary	*Malus domestica*	Rosaceae	CHOK1 (1000 μg/ml = 68.3% inhibition)	[51]
Colon	*Kadsura longipedunculata*	Schisandraceae	SW-480 (IC_{50} = 136.62 μg/ml)	[70]
Colon	*Comptonia peregrina* (L.)	Myricaceae	DLD-1 (IC_{50} = 46 μg/ml)	[106]
Colon	*Satureja khuzistanica*	Lamiaceae	SW480 (IC_{50} = 62.5 μg/ml)	[8]

Colon	1,8 cineol	---	HCT116 and RKO	[9]
Colon	*Artemisia indica*	Asteraceae	Caco-2 (IC_{50} = 19.5 μg/ml)	[11]
Colon	*Pituranthos tortuosus* (Desf.)	Apiaceae	HCT116 (IC_{50} = 1.34 μg/ml)	[54]
Colon	*Croton regelianus* and ascaridole compound	Euphorbiaceae	HCT-8 (IC_{50} = 40.0 μg/ml and 18.4 μg/ml respectively)	[97]
Colon	*Cymbopogon flexuosus*	Poaceae	502713 (IC_{50} = 4.2 μg/ml)	[107]
Colon	Eugenol	---	SNU-C5 (IC_{50} = 129.4 μM)	[89]
Colon	Geraniol and 5-fluorouracil	---	Caco-2 (IC_{50} = 250 and 0.4 μM respectively) and SW620 (IC_{50} = 330 and 2.0 μM respectively)	[96]
Colon	*Afrostyrax lepidophyllus* and *Scorodophloeus zenkeri*	Huaceae and Caesalpiniaceae (Fabaceae)	HCT116 (IC_{50} = 12.4 μg/ml and 8.5 μg/ml respectively)	[10]
Colon	*Athanasia brownii* Hochr.	Asteraceae	HCT 116 (IC_{50} = 29.53 μg/ml)	[40]
Kidney	*Platycladus orientalis* and *Prangos asperula*	Cupressaceae and Apiaceae	ACHN (IC_{50} = 121.93 and 139.17 μg/ml respectively)	[5]
Kidney	*Laurus nobilis*	Lauraceae	ACHN (IC_{50} = 78.24 μg/ml)	[67]
Kidney	*Aristolochia mollissima* rhizome and the aerial part	Aristolochiaceae	ACHN (IC_{50} = 22.3 and 33.8 μg/ml respectively)	[59]
Kidney	*Satureja khuzistanica*	Lamiaceae	Vero (IC_{50} = 31.26 μg/ml)	[8]
Leukaemia	*Cymbopogon flexuosus* and isointermedeol	Poaceae	HL-60 (IC_{50} = 30 μg/ml and 20 μg/ml, respectively)	[80]
Leukaemia	*Casearia sylvestris*	Salicaceae	HL-60 (IC_{50} = 29 μg/ml)	[42]
Leukaemia	*Artemisia indica*	Asteraceae	THP-1 (IC_{50} = 10 μg/ml)	[11]
Leukaemia	*Malus domestica*	Rosaceae	THP-1 (1000 μg/ml = 68.3% inhibition)	[51]
Leukaemia	carbazole alkaloids	---	P388 (IC_{50} = 5.00 μg/ml)	[98]
Leukaemia	*Croton regelianus* and ascaridole compound	Euphorbiaceae	HL-60 (IC_{50} = 22.2 μg/ml and 6.32 μg/ml respectively)	[97]
Leukaemia (Promyelocytic)	Eugenol	---	HL-60 (IC_{50} = 23.7 μM)	[89]
Leukaemia (mouse)	*Ocimum basilicum* L	Lamiaceae	P388 (IC_{50} = 0.0362 mg/ml)	[108]
Liver	*Schefflera heptaphylla* (L.) Frodin	Araliaceae	HepG2 (IC_{50} = 6.9 μg/ml)	[72]
Liver	*Curcuma wenyujin*	*Zingiberaceae*	HepG2 (IC_{50} = 70 μg/ml)	[109]
Liver	*Curcuma zedoaria* (Berg.) Rosc.	*Zingiberaceae*	SMMC-7721 (IC_{50} = 30.7 μg/ml)	[110]
Liver	*Patrinia scabra* Bunge	Caprifoliaceae	Bel-7402 (IC_{50} = 16 μg/ml)	[52]
Liver	Eugenol	---	HepG2 (IC_{50} = 118.6 μM) and U-937 (IC_{50} = 39.4 μM)	[89]
Liver	*Thymus citriodorus*	Lamiaceae	HepG2 (IC_{50} = 0.34% v/v)	[53]
Liver	*Artemisia indica*	Asteraceae	HEP-2 (IC_{50} = 15.5 μg/ml)	[11]
Liver	*Pituranthos tortuosus* (Desf.)	Apiaceae	HEPG2 (IC_{50} = 1.67 μg/ml)	[54]
Liver	*Kadsura longipedunculata*	Schisandraceae	HepG2 (IC_{50} = 136.96 μg/ml)	[70]
Liver	*Aristolochia mollissima* rhizome and the aerial part	Aristolochiaceae	Bel-7402 (IC_{50} = 33.1 and 49.5 μg/ml respectively) and Hep G2 (IC_{50} = 33.2 and 40.7 μg/ml respectively)	[59]
Lung	*Artemisia indica*	Asteraceae	A-549 (IC_{50} = 25 μg/ml)	[11]
Lung	*Tridax procumbens*	Asteraceae	B16F-10 *in vitro* (70.2% of inhibition for 50 μg) and *in vivo*	[61]
Lung (small cell)	*Solanium spirale* Roxb.	Solanaceae	NCI-H187 (IC_{50} = 24.02 μg/ml)	[44]
Lung	*Malus domestica*	Rosaceae	A549 (1000 μg/ml = 60.7% inhibition)	[51]
Lung	*Thymus vulgaris* L.	Lamiaceae	A549 (IC_{50} = 0.011% (v/v))	[32]
Lung	*Comptonia peregrina* (L.)	Myricaceae	A-549 (IC_{50} = 66 μg/ml)	[106]
Lung	*Xylopia frutescens Aubl.*	Annonaceae	NCI-H358M (IC_{50} = 24.6 μg/ml)	[60]

Mouth epidermal carcinoma	*Psidium guajava* L	Myrtaceae	KB (IC_{50} = 0.0379 mg/ml)	[108]
Multiple myeloma	β-caryophyllene oxide	---	U266 and MM1.S	[78]
Nasopharyngeal cancer	*Centipeda minima*	Asteraceae	CNE (IC_{50} = 5.2 μg/ml after 72 hrs)	[111]
Neuroblastoma	*Cymbopogon flexuosus*	Poaceae	IMR-32 (IC_{50} = 4.7 μg/ml)	[107]
Oral cancer	*Solanium spirale* Roxb.	Solanaceae	KB (IC_{50} = 26.42 μg/ml)	[44]
Oral cancer	*Salvia officinalis*	Lamiaceae	UMSSC1 (IC_{50} = 135 μg/ml)	[112]
Oral cancer	*Levisticum officinale*	Apiaceae	HNSCC (IC_{50} = 292.6 μg/ml)	[65]
Ovary	*Patrinia scabra* Bunge	Caprifoliaceae	HO-8910 (IC_{50} = 21 μg/ml)	[52]
Ovary	*Cymbopogon citratus*	Poaceae	Chinese Hamster Ovary (CHO)	[50]
Pancreas	*Angelica archangelica* fruits from separate locations A, B and C	Apiaceae	PANC-1 (IC_{50} = 58.4; 108.3 and 48.6 μg/ml respectively)	[71]
Pancreas	*Kadsura longipedunculata*	Schisandraceae	MIA PaCa-2 (IC_{50} = 133.53 μg/ml)	[70]
Prostate	*Xylopia frutescens* Aubl	Annonaceae	PC-3M (IC_{50} = 40 μg/ml) and *in vivo* at 37.5% of inhibition	[60]
Prostate	*Nagami kumquats*	Rutaceae	LNCaP (200 ppm = 55, 61 and 63.4 % inhibition at 24, 48, 72 h	[113]
Prostate	*Rosmarinus officinalis*	Lamiaceae	LNCaP (IC_{50} = 180.9 μg/ml)	[101]
Prostate	a-humulene	---	LNCaP (IC_{50} = 11.24 μg/ml)	[67]
Prostate	β-caryophyllene oxide	---	DU145	[78]
Prostate	*Thymus vulgaris* L.	Lamiaceae	PC-3 (IC_{50} = 0.010% (v/v))	[32]
Prostate	*O. basilicum, L. multiflora, A. conizoides, and Z. officiniale*	Lamiaceae, Verbenaceae, Asteraceae and Zingiberaceae respectively	LNCaP (0.46, 0.58, 0.35 and 0.38 mg/ml respectively) and PC3 (0.45, 0.30, 0.49 and 0.42 respectively)	[36]
Skin (melanoma)	*Athanasia brownii* Hochr.	Asteraceae	A375 (IC_{50} = 19.85 μg/ml)	[40]
Skin (melanoma)	*Afrostyrax lepidophyllus* and *Scorodophloeus zenkeri*	Huaceae and Caesalpiniaceae (Fabaceae)	A375 (IC_{50} =20.6 μg/ml and 17.7 μg/ml respectively)	[10]
Skin (melanoma)	*Casearia sylvestris*	Salicaceae	A2058 (IC_{50} = 41.1 μg/ml)	[42]
Skin (melanoma)	*Curcuma zedoaria* (Berg.) Rosc.	*Zingiberaceae*	B16BL6 (IC_{50} = 41.8 μg/ml)	[110]
Skin (melanoma)	*Croton regelianus* and ascaridole compound	Euphorbiaceae	MDA-MB-435 (IC_{50} = 47.3 μg/ml and 10.5 μg/ml respectively)	[97]
Skin (melanoma)	*Schefflera heptaphylla* (L.)	Araliaceae	A375 (IC_{50} = 7.5 μg/ml)	[72]
Skin (amelanotic)	*Cupressus sempervirens* ssp. pyramidalis	Cupressaceae	C32 (IC_{50} = 104.90 μg/ml)	[5]
Skin (amelanotic)	*Laurus nobilis*	Lauraceae	C32 (IC_{50} = 75.45 μg/ml)	[67]
Stomach	*Nigella sativa* seeds	Ranunculaceae	SCL, SCL-6, SCL-37'6, NUGC-4 and Kato-3 (IC_{50} = 155.02; 185.77; 120.40; 384.53 and 286.83 respectively)	[114]
Uterus	*Casearia sylvestris*	Salicaceae	Siha (IC_{50} = 23.9 μg/ml)	[42]

of *Neolitsea variabillima* [41] and *Casearia sylvestris* [42] had cytotoxic activity against human melanoma cancer.

Breast cancer

EOs of *A. lepidophyllus* and *S. zenkeri* inhibited the growth of human breast adenocarcinoma MDA-MB 231 cell line [10]; likewise, EOs extracted from leaves of *Satureja khuzistanica* Jamzad [8], *Casearia sylvestris* [42], *Cedrelopsis grevei* [43] and *Solanium spirale* Roxb [44] significantly reduced cell viability and/or increased cytotoxicity of MCF7 cells in a dose-dependent manner. Human breast cancer cell lines T47D, MCF7, MDA-MB-231 were sensitive to the treatment with *Boswellia sacra* EO with reduced cell viability and elevated cell death [45]. *S. erianthum* leaf volatile oil demonstrated potent inhibitory activity against human breast Hs 578T tumor cells [31].

Colon cancer

Geraniol, a monoterpene found in EOs of various fruits and herbs has been proposed to represent a new class of agents for cancer chemoprevention, as it has antiproliferative activity on Caco-2 colon cancer cells [46]. EOs of *A. lepidophyllus*, *S. zenkeri* [10] and *Athanasia brownii* exhibited a strong growth-inhibitory effect on human colon carcinoma HCT116 cell line [40]. EO isolated from the leaf of *Neolitsea variabillima* exhibited cytotoxic activity against human colon cancer [41]. EO from *Satureja khuzistanica* significantly reduced cell viability of SW480 cell line in a dose-dependent manner [8]. Volatile oil was obtained from blood oranges showed pro-apoptotic and anti-angiogenesis potential on colon cancer cells [47]. EO of *Artemisia campestris* exhibited significant antitumor activity against the HT-29 cells of colon cancer deserve further research into the chemoprevention and treatment [48]. Thymoquinone inhibited the proliferation of a panel of human colon cancer cells (Caco-2, HCT-116, LoVo, DLD-1 and HT-29), without exhibiting cytotoxicity on normal human intestinal FHs-74Int cells [49].

Ovary cancer

EO of *Cymbopogon citratus* was toxic against Chinese Hamster Ovary cells [50]. *Guatteria pogonopus* leaves EO showed significant *in vitro* and *in vivo* antitumor activity on ovarian adenocarcinoma OVCAR-8 [35]. The essential oil of leaves of *Malus domestica* at 1000 µg/ml has resulted 68.3% of inhibition of CHOK1 cells [51]. The volatile oil from the roots of *Patrinia scabra* Bunge showed the strongest inhibitory effect on human ovarian carcinoma cells HO-8910 [52].

Liver cancer

EOs from *Thymus citriodorus* [53], *Artemisia indica* [11] and *Pituranthos tortuosus* (Desf.) [54] leaves have strong toxic effects on liver cancer cells HepG2. Su et al. [41] showed that EO isolated from the leaf of *N. variabillima* exhibited cytotoxic activity against human liver cancer. *Zanthoxylum schinifolium* essential oils induced apoptosis of human hepatoma HepG2 cell line is dependent of the production of ROS but not on caspase activation [55].

Uterus and cervix cancers

Leaves of *Casearia sylvestris* showed cytotoxic activity on uterus carcinoma Siha cell line [42]. The leaf and stem EOs of *Liquidambar styraciflua* L. induce low cytotoxic activity on cervix cancer cells HeLa [56]. An identical effect was observed with *Schinus terebinthifolius* Raddi [57]. Furanodiene, a sesquiterpene extracted from the essential oil of the rhizome of *Curcuma wenyujin*, inhibited the growth of uterine cervical (U14) tumors in mice [58]. The rhizome and the aerial part of *Aristolochia mollissima* has a significantly stronger cytotoxicity on human cervix carcinoma cell line HeLa [59].

Lung cancer

The *Xylopia frutescens* leaf EO of displayed *in vitro* and *in vivo* cytotoxicity on bronchoalveolar lung carcinoma cell line NCI-H358M [60]. *In vivo* activity was shown by EOs of *X. frutescens* [60], *Guatteria pogonopus* [35] and *Neolitsea variabillima* [41]. Investigations showed significant effects of the EO of *Tridax procumbens* L in preventing lung metastasis by B16F-10 cell line in C57BL/6 mice [61]. EO from the aerial parts of *A. indica* had concentration dependent growth inhibition of A-549 cell line [11]. Vapor of volatile oil compounds obtained from *Litsea cubeba* seeds killed human NSCLC cells, A549, through the induction of apoptosis and cell

cycle arrest [62]. Vapor generated from the combined oils deactivated Akt, a key player in cancer cell survival and proliferation, and Mdm2, which induced overexpression of p53 which in turn upregulated p21 expression [62]. EO of *Solanium spirale* Roxb. leaves showed significant cytotoxicity against NCI-H187 cells [44].

Oral cancer

EO isolated from the leaf of *N. variabillima* exhibited cytotoxic activity against human oral cancer [63]. EO of the leaves of *Solanium spirale* Roxb. showed significant cytotoxicity against KB cell line [44]. Treatment with *Pinus densiflora* leaf EO at 60 μg/ml strongly inhibited proliferation and survival of YD-8 oral squamous cell carcinoma by apoptosis [64]. Indeed, this treatment led to the activation of caspase-9, PARP cleavage, down-regulation of Bcl-2, and phosphorylation of ERK-1/2 and JNK-1/2 in YD-8 cells [64]. *Salvia officinalis* EO reduced UMSSC1 cell viability by regulating the aryl hydrocarbon receptor signaling, cell cycle (G1/S checkpoint) transition, and p53 signaling [65]. *Levisticum officinale* EO inhibits human HNSCC growth by modulating extracellular signal-regulated kinase 5 (ERK5), integrin-linked kinase (ILK), virus entry via endocytic pathways and p53 pathway [65].

Leukemia

Leaves of *N. variabillima* [41] and *Casearia sylvestris* [42] showed cytotoxic activity on leukemia HL-60 cell line while EO from *A. indica* exhibited concentration dependent growth inhibition of THP-1 cell line [11]. *Juniperus excelsa* fruit essential oil as well as *Juniperus oxycedrus*, *Cedrus libani*, and *Pinus pinea* wood EOs showed cytotoxic activity against drug-sensitive CCRF-CEM and multidrug-resistant P-glycoprotein-expressing CEM/ADR5000 leukemia [66]. EO from *Malus domestica* leaves at 1000 μg/ml has resulted 65.7% of inhibition of human acute monocytic leukemia cell THP-1 [51].

Kidney cancer

Satureja khuzistanica significantly reduced cell viability of Vero cell line in a dose-dependent manner [8]. EO of *Platycladus orientalis*, *Prangos asperula* [5] and *Sideritis perfoliata* [67] exerted cytotoxic activity on renal adenocarcinoma cell line ACHN. Rhizome and aerial parts of *Aristolochia mollissima* showed cytotoxicity activity on ACHN cells [59].

Bone cancer

Volatile oil from *Pyrolae herba* demonstrated potent antitumor activity against SW1353 cells in dose- and time-dependent manner. Furthermore, these EOs decreased the number of cells entering the S phase and caused a reduction in the expression of cyclin D1, cyclin-dependent kinase (CDK)4 and CDK6, whereas it caused an increase of the expression of p21 [68].

Pancreas cancer

Human pancreas cancer cells were sensitive to EO fractions prepared from *Boswellia* species gum resins treatment with suppressed cell viability and increased cell death. In fact, EO activates the caspase-dependent apoptotic pathway, induces a rapid and transient activation of Akt and Erk1/2, and suppresses levels of cyclin D1 cdk4 expression in cultured cancer cells [69]. EO from stem bark of *Kadsura longipedunculata* exhibited cytotoxic activity against MIA PaCa-2 cell line of human pancreas carcinoma [70]. EOs from *Angelica archangelica* fruits collected in Reykjavik, from various locations showed cytotoxic activity independent of the quantity of their main components on PANC-1 human pancreas cancer cells [71].

Skin cancer

EO of *Schefflera heptaphylla* (L.) Frodin and its major compound beta-pinene ((-)-beta-pinene and (+)-beta-pinene) showed significant antiproliferative activity against A375 cancer cell lines [72].

Mode of action

Due to their high heterogeneous compositions, it is difficult to define a unique mechanism of action for EOs. Indeed, a molecule could have an effect on one type of tumor and not on others. For example, Murata et al. [9] showed that 1,8-cineole/eucalyptol induces apoptosis of human colon cancer cells. Conversely, this molecule has no effect on prostate cancer and glioblastoma cell survival [36]. Moreover, depend-

ing on the enrichment of the active compounds, various mechanisms could be observed, such as an effect on the cell cycle, cell growth, and/or apoptosis.

Indeed, generally biological activity of an EO is related to its chemical composition, to the major functional groups of compounds (alcohols, phenols, terpene compounds and ketone). However the less present compounds could also be of importance as the various molecules could synergistically act with the major compounds [73]. For exemple the single exposure to limonene or linalyl acetate found enriched in bergamot (*Citrus bergamia* Risso et Poiteau) does not replicate the effect of bergamot EO on caspase-3 activation, PARP cleavage, DNA fragmentation, cell shrinkage, cytoskeletal alterations, together with necrotic and apoptotic cell death [74]. Despite that fact and for a didactic aspect, it has seemed interesting however to present the molecular effects of some example of isolated compounds from EOs.

Terpenes and terpenoids

Edris [75] reported that β-elemene, a sesquiterpene from *Nigella sativa*, could inhibit the growth of laryngeal cancer cells by activating caspase-3 cleavage and decreasing the accumulation of eukaryotic initiation factors eIF-4E and 4G, basic fibroblast growth factor (bFGF) and vascular epithelial growth factor (VEGF).

In ginger, gingerol down-regulates the antiapoptotic protein Bcl-2 and enhances the pro-apoptotic protein Bax, while gingerdione is an effective anti-tumor agent in human leukemia cells by inducing G1 arrest, through the down-regulation of cyclin D2, cyclin E and cdc25A and the up-regulation of CDK1 and p15. Gingerdione also decreases *Bcl-2* accumulation and activates caspase-3 cleavage [76]. The monoterpene 1,8-cineole/eucalyptol induces specific apoptosis, and not necrosis, on human colon cancer cell lines HCT116 and RKO. The treatment with 1,8-cineole was associated with the inactivation of surviving, and Akt and activation of p38. These molecules induce the cleavage of PARP and caspase-3, finally causing apoptosis [9]. D-Limonene is toxic on V79 cells in a dose-dependent manner [77]. In fact, this drug has a direct effect on dividing cells, preventing assembly of mitotic spindle microtubules. This affects both chromosome segregation and cytokinesis, resulting in aneuploidy that in turn can lead to cell death or genomic instability [77].

β-caryophyllene oxide, a sesquiterpene isolated primarily from the EOs of medicinal plants such as guava (*Psidium guajava*) and oregano (*Origanum vulgare* L.), suppresses constitutive STAT3 activation in multiple myeloma, breast and prostate cancer cell lines, with a significant dose- and time-dependent effects observed in multiple myeloma cells [78]. The suppression was mediated through the inhibition of activation of upstream kinases c-Src and JAK1/2. Indeed, β-caryophyllene oxide induces the expression of tyrosine phosphatase SHP-1 that correlates with the down-regulation of constitutive STAT3 activation [78].

Geraniol, present in the EOs of many aromatic plants, has *in vitro* and *in vivo* antitumor activity against several cell lines [79]. In fact, geraniol alters several lipid metabolic pathways of HepG2 cells such as the mevalonate pathway and the phosphatidylcholine biosynthesis, which results in cell growth inhibition, cell cycle arrest occurring at the G0/G1 interphase, and increased apoptosis [79].

Isointermedeol, a major sesquiterpene found in EO extracted from *Cymbopogon flexuosus*, induces apoptosis in human leukaemia HL-60 cells [80]. Indeed, isointermedeol activates apical death receptors TNFR1, DR4 and caspase-8 activity. Simultaneously, both increase the expression of mitochondrial cytochrome c protein with its concomitant release to cytosol leading to caspase-9 activation. Further, Bax translocation and decrease in nuclear NF-kappaB expression predict multi-target effects of isointermedeol while both appeared to follow similar signaling apoptosis pathways [80].

Furanodiene, a sesquiterpene extracted from *Curcuma wenyujin*, enhances mitochondrial transmembrane depolarization, release of mitochondrial cytochrome c, activation of caspases-3 and cleavage of PARP [81]. Furanodiene mediated mitochondria-caspase apoptotic pathway also involves activation of p38 and inhibition of ERK mitogen-activated protein kinase (MAPK) signaling [81].

Collectively, thymol induces a cytosolic Ca^{2+} rise by inducing phospholipase C- and protein kinase C-dependent Ca^{2+} release from the endoplasmic reticulum and Ca^{2+} entry. Likewise

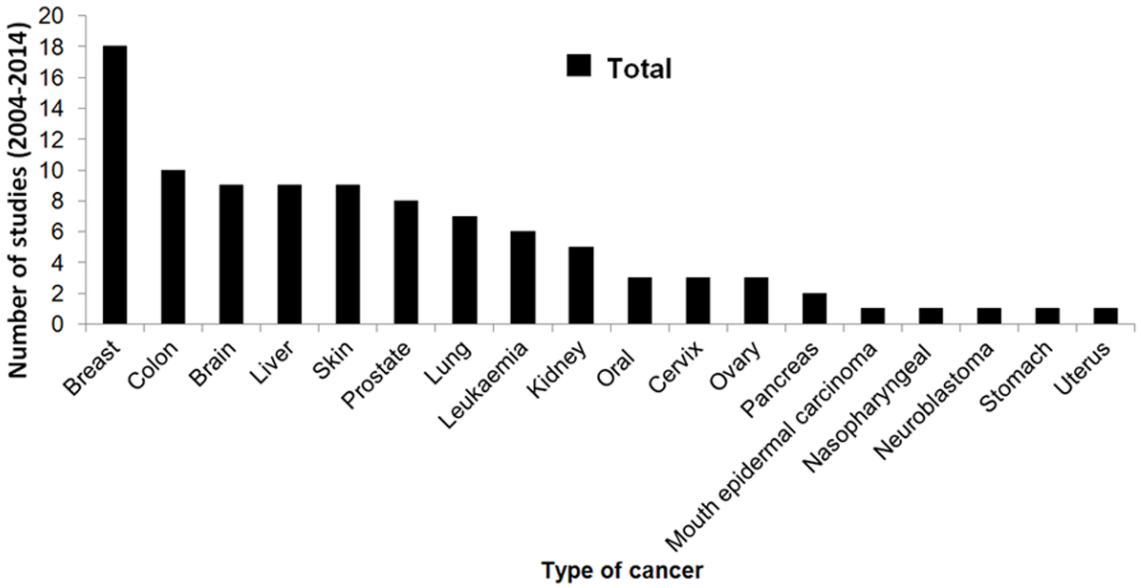

Figure 5. Total of studies with EOs and compounds from 2004 to 2014 on various types of cancer.

Liang and Lu [82] showed that carvacrol has the same effect on Ca^{2+} and cell viability as thymol, even though carvacrol effect could also involve ROS-mediated apoptosis.

Terpenoids thymoquinone, which is the major compound of black seed (*Nigella sativa*) oil, traditionally used in Mediterranean and arab medicine, possesses significant anticancer effects in various cancer models [83]. It was previously shown that thymoquinone induces apoptosis through p53-dependent pathways in human colon cancer cells and animal models [84, 85]. β-Elemene arrests the cell cycle and induces apoptosis of lung cancer cells [86].

Aromatic compounds

Carvacrol induces apoptosis and activation of ROS and caspase-3 [87]. Indeed this monoterpenoid raises intracellular concentration of Ca^{2+} by activating a PKC-sensitive, non store-operated Ca^{2+} channels. Carvacrol also induces ROS- and caspase-3-associated apoptosis of OC_2 human oral cancer cells [87].

Eugenol is an essential oil mainly found in buds and leaves of clove *Syzygium aromaticum* (L.) inhibits the cell proliferation and induces the apoptosis in human MCF-7 breast cancer cells [88]. This biological activity is correlated to its activity as an estrogen receptor antagonist. In this article, we present the construction and validation of structure-based virtual screening. This biological property has been correlated to its activity as an estrogen receptor antagonist [88]. Found also in EO of *Eugenia caryophyllata*, eugenol induces apoptosis of human promyelocytic leukemia HL-60 cells [89]. This phenomenon has been explained by the translocation of Bax from the cytosol to the mitochondria, the reduction of Bcl-2 protein level and cytochrome c release into cytosol, thus leading to sequential activation of caspase-9 and caspase-3 [89].

Indolizine derivatives could also be anticancer agents [90]. For example, 4-(3,4)-dihydroxyphenyl)-2-phenylpyrido[2,3-b]indolizine-10-carbonitrile has a strong cytotoxicity on all tested colorectal cancer cell lines, and this at concentrations that have no effect on fibroblasts [90]. Cell-cycle analysis indicated that pyrido [2,3-b] indolizines could affect cell-cycle progression by accumulating treated cells in S- and G2/M-phases [90].

Conclusion and future callenges

According to the World Health Organization [91], incidence and mortality of cancer is increasing worlwide. The various treatments require a careful selection of one or more of existing modalities such as surgery, radiotherapy and systemic therapy. This selection should be based on evidence of the best existing treatment given the resources available. However in

developing countries such as Burkina Faso, it is not always possible to have a correct access to anticancer molecules. Plants are hence a potential source of drug discovery and development of cancer chemoprevention or treatment [92]. They could thus provide a hope for finding anticancer molecules available and efficient for the treatment of persons with cancer (**Figure 5**). This review shows that more and more studies are necessary to carry out on the anti-cancer activity of EOs as nature is a rich source of biological and chemical diversity. The unique and complex structures of natural products cannot be obtained easily by chemical synthesis. Interest in medicinal plant research has increased in recent years, especially for the treatment of cancer [6, 93]. Cytotoxicity has been reported for many EOs [94, 95]. However, very few studies have been done on the combination of EOs and their major compounds to find putative synergistic beneficial effects, as the association of 5-fluorouracil and geraniol in both SW620 and Caco-2 cells of human colonic carcinoma [96].

However, when EOs are extracted from aromatic plants, there is a long road before using them as a drug. The pharmaceutical research phase is mandatory to identify new molecular targets, both in cell culture and in animal models, and to engineer more efficient molecules from the natural compound. To help in accelerating the molecule identification it is important to remember that all ancient civilizations have developed alongside agriculture, herbal medicine and eminent physicians of the past were usually also herbalists. Nobody could deny that chemotypes of EOs have a wide spectrum of action on various therapies, even though the molecular mechanisms and events need to be identified as well.

The joint activity between chemistry, biochemistry, biology, medicine, pharmacy and botany to correctly identify these chemical constituents is thus fundamental. Finding new active EOs for the treatment of cancers is a challenge. Using it in Human to treat is promise.

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Disclosure of conflict of interest

None.

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