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„Biological activities of essential oils: An update

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Abstract in German

Viele neue Forschungsergebnisse, die anti-mikrobielle, antiinfektive, verbesserte Penetration, vasodilatorische, cytotoxische, anti-virale und antinociceptive Wirkungen betreffen, wurden in den letzten vier Jahren veröffentlicht.

Die vorliegende Diplomarbeit ist eine Zusammenfassung von neuen Forschungsergebnissen bezüglich der biologischen Aktivität von ätherischen Ölen.

Abstract

Many new research results, regarding anti-microbial, anti-inflammatory, penetration enhancing, vasodilatory, cytotoxic, anti-viral and anti-nociceptive effects of essential oils have been published in the last four years.

This master thesis provides a summary of these new researches results concerning the biological activity of essential oils.

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Introduction

This master thesis deals with an overwiew of the research results of antibacterial, antiviral, antinociceptive, anti-inflammatory, vasodilatory and penetration enhancing activity of essential oils and covers the literature from 2009 to March 2014. It is well known, that essential oils exert many effects in the human and animal body. Many authors before have described several biological activities. This treatise should afford an overview of the research results concerning the above mentioned topics from 2009 to 2014 following earlier essays. The treatment of common disease and indispositions, rheumatoid arthritis, pain, high blood pressure, cancer and many more, with alternative methods such as essential oils, is still current. Because of a high rate of resistances against common treatment science is in the quest of alternative or at least complementary treatment opportunities.

1 Antibacterial Activity

In a study about anti-biofilm activity of lemongrass and grapefruit essential oil against *Staphylococcus aureus*, Adukwu et al. (2012) studied the antibacterial activity of lemongrass (*Cymbopogon flexuosus* Stapf.) (Poaceae), and grapefruit (*Citrus paradisi MACF*) (Rutaceae). They used five different strains of *St. aureus* (three MSSA strains and two MRSA strains) for testing the antibacterial activity, with the disc diffusion test and some biofilm methods. Tests showed that lemongrass and citral, the main component of lemongrass essential oil (EO) possessed the highest activity against all strains of *St. aureus*. Concentrations between 0.03% and 0.06% (v/v) were inhibiting growth of all five *S. aureus* and at 0.125% (v/v) lemongrass EO operated as bactericide. Grapefruit EO showed higher Minimum Inhibitory Concentration (MIC) than lemongrass EO for all the strains of *St. aureus*. Between 0.5 and 2% (v/v) the grapefruit EO indicated bacterial growth inhibiting, bactericidal activity was observed between 2% and 4% (v/v).

Artemisia spicigera C. Koch (Asteraceae) EO was found to be active against Gram-positive and Gram-negative bacteria. The aerial parts of *A. spicigera* were collected from different parts of East Azerbaijan. Eight different EOs were tested with the agar-gel diffusion method against *Escherichia coli*, *Enterobacter aerogenes, Serratia marcescens, Bacillus cereus, Citrobacter amalonaficus, St. aureus, Staphylococcus saprophyticus* and *Bacillus megaterium*. Antibacterial tests showed good activity against the studied bacterial strains. Quality and quantity of the EO depend on ecological conditions and the way the EO was extracted. Different populations showed different activities against tested bacterial strains. While the EO of population nr.1 (geographical character: N: 37°41’5”; E: 45°52’29”) showed higher inhibition zones against *E.coli, E.aerogenes, S. marcescens* and *St. aureus*, the EO of population Nr.5 (geographical characters: N: 33°09’24,9”; E: 46°39’0,2”) indicated higher inhibition zones against *St. saprophyticus, B. megaterium* and *B. cereus*. Their effects are also more outstanding than studied standard antibiotics (Chehregani, et al., 2013).

The EO from *Launaea resedifolia* L. (Asteraceae) was tested for its antibacterial activity against *E. coli, St. aureus, St. intermedius, Proteus mirabilis, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The authors used the disc diffusion test and MIC for testing the EO. The efficacy of the EO was shown to depend on the size of the inhibiting zone. It was found that *St. aureus* (inhibition zone of 37mm) was the most sensitive bacterial strain for *L. resedifolia* EO. *St. intermedius, K. pneumoniae, St. pyogenes* and *P. mirabilis* were found to be sensitive as well, as they showed inhibition zones of 29, 27, 23 and 20mm. *E. coli* and *P. aeruginosa* also reacted moderately sensitive on the treatment with EO (Inhibition zone of 15 and 12mm). (Zellagui, et al., 2012a)

Kavoosi et al. (2013a) found, that the EO of *Carum copticum* L. (Apiaceae) significantly reduced the growth of Gram-positive and Gram-negative bacteria. MIC of carum oil for *Salmonella thyphi, E. coli, St. aureus,* and *B. subtilis* were 78±8, 65±7, 14±3 and 5±2 µl/ml, respectively.

Daucus muricatus L. (Apiaceae) EO was studied for the antibacterial activity against nine pathogenic microorganisms (*B. subtilis, Listeria monocytogenes, B. cereus, St. aureus, P. aeruginosa, E. faecalis, K. pneumoniae, E. coli*) using the paper disc agar-diffusion technique. The EO showed highest activity against *St. aureus* (zone of inhibition: 22mm), while the lowest activity was exhibited against *E. coli. B. cereus* and *L. monocytogenes* were also sensitive against *D. muriaticus* EO with zones of inhibition ranging from 12 to 16 mm. In general, root oil of *D. muriaticus* showed higher activity against the tested microorganism than the EO of the aerial parts (Bendiabdellah, et al., 2012).

Zomorodian et al. (2012) studied the antimicrobial activity of *Nepeta cataria* L. (Lamiaceae) EO against *E. coli, St. aureus, Shigella flexneri, B. cereus* and *P. aeruginosa.* The EO inhibited growth of all Gram-positive bacteria and it further exhibited bactericidal activity against Gram-positive bacteria at a concentration ranging from 0.5 to 8 µL/ml. The EO also showed bacteriostatic and bactericidal activity against

Shigella and *Salmonella* species at concentrations of 0.25-2 µl/ml and 0.5-8 µl/ml.

The EO of *Eucalyptus globulus* Labill. (Myrtaceae) was tested against two clinical isolated strains of *E. coli* and *St. aureus*. The agar disc diffusion method was used to determine the antimicrobial activities. The addition of *E. globulus* EO to the bacterial strains caused growth inhibition on both microorganism. Furthermore, the inhibition was greater on *E. coli* than observed on *St. aureus* (Bachir Raho & Benali, 2012).

Hypericum rochelii Griseb. & Schenk and *Hypericum umbellatum* A. Kern. (Hypericaceae) were studied for their antibacterial activity against five bacterial strains (*B. subtilis, St. aureus, E. coli, Salmonella abony, P. aeruginosa*) using broth microdilution assay. *H. rochelii* EO was the most active *against St. aureus. H. umbellatum* EO also indicated moderate antibacterial activity (Dordevic, et al., 2013).

Ten different strains of Gram-negative (*E. coli, Salmonella sp., Enterococcus cloacae, K. pneumoniae, P. aeruginosa*) and Gram-positive bacteria (*B. subtilis, B. cereus, Micrococcus luteus, St. aureus*) were tested to be sensitive against *Thymus maroccanus* Ball and *Thymus broussonetii* Boiss (Lamiaceae) EO. The antibacterial activity of the mentioned EOs were settled using the disc diffusion agar method. Furthermore, MIC was determined using the macrodilution broth method. The tested EOs showed a wide antibacterial spectrum as they produced inhibition zone diameters ranging from 9 to 42 mm. The inhibition zone diameters were sometimes even higher than those achieved with general antibiotics. Gram-positive bacteria were found to be more sensitive against the above mentioned EOs than Gram-negative, while *P. aeruginosa* proved to be the most resistant. Synergistic interaction of antibiotics with the two *Thymus* EOs were determined by the checkerboard test. 80 combinations of the EOs and four antibiotics (ciprofloxacin, gentamycin, pristinamycin and cefixim) were studied. The best antibacterial effect was achieved with the combination of *T. maroccanus* and ciprofloxacin. The total synergistic

effect of this combination was observed for Gram-positive and Gram-negative bacteria (Fadli, et al., 2012).

De Azeredo et al. (2012) investigated the cytotoxic effect of essential oils from *Origanum vulgare* L. and *Rosmarinus officinalis* L. (both Lamiaceae) on *Aeromonas hydrophila*. The EOs, used alone and in combination, severely inhibited cell viability of *A. hydrophila.*

Melaleuca species were found to have several antibiotic activities. The essential oils exhibited inhibitory activity against *St. epidermidis* which is a Gram-positive pathogen. Gram-negative bacteria, such as *E. coli* were also affected by the oil of *M. armillaris* Sm and *M. acuminate* F. Muell. (Myrtaceae), the latter of which was more active than *M. armillaris* oil (Amri, et al., 2012).

The EO of *Ferula assa-foetida* Linn. (Apiaceae) oleo-gum resin was examined for its antibacterial activity in dependence of collection time. Three different samples of EO, of plants, collected at different times, were produced and investigated. All EOs significantly decreased the growth of Gram-positive and Gram-negative bacteria. The various EOs showed different activity in relation to growth inhibition of bacterial strains (Kavoosi & Rowshan, 2013b).

E. coli, two different strains of *St. aureus, P. aeruginosa, Neisseria gonorrhoeae, B. subtilis* and *E. faecalis* were investigated for their sensitivity against *Syzygium cumini* Linn. (Myrtaceae) leaves EO. The EO contained antibacterial activity against both Gram-positive and Gram-negative bacterial strains (Mohamed, et al., 2013).

Tunesian *Conyza sumatrensis* (Retz.) E. Walker (Asteraceae) essential oil was found to have highest antimicrobial activity against *E. faecalis and St. aureus*. Generally, essential oil of the aerial parts, especially the leaf oil, showed higher inhibiting activity than root oil (Mabrouk, et al., 2013).

Valencia Orange (*Citrus sinensis* L.) (Rutaceae) EO was studied for antibacterial activity against Methicilin-susceptible *St. aureus* and

Vancomycin intermediate resistant strains. The authors used terpeneless cold-pressed Valencia orange oil (CPV). Keratinocytes infected with *St. aureus* as a model for soft part and skin infections were treated with CPV (0.1% or 0.2%). After 3h of incubation with 0.2% CPV *St. aureus* was undetectable (Muthaiyan, et al., 2012).

An antibacterial activity test was run on essential oils of leaves of *Ferula vesceritensis* Coss et Dur. (Apiaceae) using the disc diffusion method. Investigated were four human pathogens (*E. coli, K. pneumonia, S. aureus, P. aeruginosa*). *F. vesceritensis* inhibited growth of all four microorganisms. Inhibiting Zone Diameters increased proportionally with the increase of concentrations (Zellagui, et al., 2012).

The EO of *Ruta* species were tested against their antimicrobial activity by the presence of inhibition zones, zone diameters and MIC values. Results exhibited low in vitro antimicrobial activity *for E. cloacae, E. faecalis, Acinetobacter baumanii, B. cereus, E. coli, Citrobacter freundii, P. aeruginosa, K. pneumonia, Listeria monocytogenes, Proteus mirabilis, St. aureus, Salmonella typhi* (Haddouchi, et al., 2013).

*Mentha suaveolens subsp. Timija (*Briq.) Harley (Lamiaceae) is known as mint timija in Moroccan folk medicine and has been used for the treatment of coughs, bronchitis, ulcerative colitis and much more. Kasarati et al. (2013) cultivated and tested the species for its antibacterial activity. They used disc diffusion and MIC tests against several pathogenic bacteria. The EO of cultivated mint timija featured strong antibacterial activity (MIC 0.93mg/ml). Gram-positive and Gram-negative bacteria reacted equally sensitive to the EO.

The antibacterial activity of the EO of *Pelargonium graveolens* L`Her (Geraniaceae) and *Vitex agnus-castus* L. (Verbenaceae) was investigated against six bacterial species (*L. monocytogenes, S. enteritidis, P. aeruginosa, E. coli, St. aureus* and *B. subtillis*). The disc diffusion method showed inhibition zones ranging from 42±3,2mm to 9.5±0,7mm for the EO of *P. graveolens* except for *S. enteritidis* and *L. monocytogenes*, which showed no sensitivity against Pelargonium EO.

V. agnus-castus EO exhibited no activity against *E. coli* and *L. monocytogenes* but for the other four strains inhibition zones ranged from 50.0±0.0 to 9.0±0.0. *St. aureus* was exposed to be the most sensitive strain for *P. graveolens* and *V. agnus-castus* EO (Ghannadi, et al., 2012).

Cunha et al. (2013) studied the inhibitory effect of the EO of different parts of *Cassia bakariana* Craib. (Fabaceae) on aerobic and anaerobic pathogens. The leaves and bark oils showed strong antibacterial activity against both aerobic and anaerobic bacteria (MIC ranging from 62.5 to 125 µg/ml). The EOs of *C. bakariana* leaves and barks have indicated promising activity against oral pathogens, including *St. mutans*, the main etiological agent of dental caries.

Antibacterial activities of the EOs of three ecotypes of *Zataria multiflora* Boiss. (Lamiaceae) were tested against several Gram-positive and Gram-negative bacterial strains. At a concentration of 0.12-4 µl/ml the EOs operated as growth inhibiting on Gram-positive cocci. Besides, the EOs showed bactericidal activity at concentrations of 1-8 µl/ml for all tested Gram-positive cocci. In addition all used strains of *E.coli* and about half of the isolated *P. aeruginosa* strains were also sensitive to the EOs of *Z. multiflora* (Zomorodian, et al., 2011).

Bacillus subtillis, E. coli, Raoultella planticola, K. pneumoniae, Micrococcus luteus, Salmonella typhimurium, two strains of *St. aureus, Streptococcus mutans* and *P. aeruginosa* were studied for their sensitivity against fruit EOs of two Cameroonian *Zanthoxylum* species (Rutaceae). The in-vitro screening was performed by disc diffusion and MIC was determined. *Zanthoxylum zanthoxyloides* Lam. inhibited growth of six of the ten tested bacterial strains. Inhibition zone diameters ranged from 8-12mm. The most sensitive bacterial strain was Gram-negative *K. pneumonia* (12mm), whereas other species showed no antibacterial interaction. The EO of *Z. zanthoxyloides* also showed significant antimicrobial activity against Gram-negative *S. typhimurium* and Gram-positive *B. subtillis*. Overall, the EO of *Z. zanthoxyloides* was

more active against Gram-positive than Gram-negative bacteria (Misra, et al., 2013).

The EO of *Trachyspermum copticum* L., an annual plant of the Iranian flora, and *Satureja hortensis* L. were investigated for their antimicrobial activity against 15 microbial strains. MIC and MLC were performed with micro broth dilution assay. The MIC values of the two oils ranged from 0.06 to 8µl/ml, whereas *K. pneumonia* was the Gram-positive bacteria most sensitive to both oils. *Str. sanguis*, *Str. salivarius* and *St. aureus* were more susceptible than *Sh. flexeneri* and *Sh. dysantri*. In general, the antimicrobial activity of *T. copticum* was higher than that of *S. hortensis* oil (Mahboubi & Kazempour, 2011).

Eugenol is a component of many EOs especially of clove oil, nutmeg, cinnamon and bay leaf. Devi et al. (2013) found that eugenol acts growth inhibiting and bactericidal on *Proteus mirabilis,* a nosocomial pathogen. The antibacterial activity of eugenol against *P. mirabilis* was examined by the disc diffusion method. Ciprofloxacin acted as positive control. Eugenol, at concentrations of 1 and 10% (v/v) with zones of Inhibition of 8 and 11 mm respectively showed promising bactericidal activity. In comparison, Ciprofloxacin (500ng/ml) produced zones of inhibition of 13mm.

An experimental in-vitro study was carried out to evaluate the antibacterial activity against of *Rosmarinus officinalis* L., *Origanum syriacum* L.*, Thymus syriacus* Boiss*, Salvia palaestina Beth., Mentha Piperita* L. *and Lavandula stoechas* L. *Brucella melitensis*. The EOs of these plants were used alone and in combination with some antibiotics. *O. syriacum* and *T. syriacus* demonstrated the highest activity against *B. melitensis*. The MIC of the EOs were 3.125µl/ml and 6.25 µl/ml, respectively. The combination of levofloxacin with *T. syriacus* increased the bactericidal activity of the EO (Al-Mariri & Safi, 2013). *O. syriacum. Majorana hortensis* Moench, *Rosmarinus officinalis, Cymbopogon citratus* Stapf., *Thymus vulgaris* and *Artemisia annua* were examined for their antibacterial activity against *Listeria innocua* (CECT 910). The agar disc diffusion method was used for investigation. Pure *C. citratus*

EO showed the highest activity against *L. innocua* with diameters of the inhibition zone of 49.00 ± 5.66mm. Except for *Artemisia annua* all EOs showed antibacterial activity with diameters of inhibition zones ranging from 13.00±0.00 to 40.00±0.00mm. Even concentrations of 6.25% EOs showed promising antibacterial activity except for *R. officinalis* and *A. annua* (Viuda-Martos, et al., 2010).

Sfeir et al. (2013) found that the EOs of *Cinnamamum verum* J. S. Presl (Lauraceae), *Cymbopogon citratus* Stapf. (Poaceae), *Thymus vulgaris* CT thymol, *O. compactum* and *S. montana* have high activity against *Str. pyogenes* with diameters of inhibition zones ranging from 48.0 to 35.0 mm. *Str. pyogenes* was also sensitive against the EO of *Eugenia caryophyllus* (Spreng.) Bullock & S. G. Harrison (Myrtaceae) and *Cymbopogon martinii* (Roxb.) Wats. with zones of inhibition of 18.3 and15.3 mm, respectively. Moderate activity was found for the EOs of *Cinnamomum camphara* CT linalool*, Mentha piperita*, *L. stoechas* L., *Melaleuca cajeput*, and *Maleleuca alternifolia* Cheel with diameters of inhibition zones ranging from 13.0 to 9.0mm (Sfeir, et al., 2013).

Two different EOs of *Chromolaena laevigata* (Lam.) R. M. King & H. Rob. (Asteraceae) (flowering and fruiting stage) were investigated for their antibacterial activity. Used bacterial strains were *St. aureus*, *P. aeruginosa* and *E. coli*. Both EOs showed strong antibacterial activity against all three bacteria. The EO from plants in their fruiting stage showed higher antibacterial activity (Murakami, et al., 2013).

The antimicrobial activity of cinnamon bark, lavender, marjoram, tea tree, peppermint EOs combined with ampicillin, piperacillin, cefazolin, cefuroxime, carbenicillin, ceftazidime, and meropenem was investigated against β-lactamase-producing *E.coli*. FIC (fractional inhibitory concentration) values were the results of the trial. It was found that peppermint EO improved the activity of piperacillin against multidrugresistant *E. coli* strains (FIC: 0.31) compared with piperacillin alone. Also the used dose of meropenem can be reduced when combined with peppermint oil (FIC: 0.26) (Xi Yap, et al., 2013).

2 Antiviral activity

The inhibition of the replication of HSV-1 (Herpes Simplex Virus) was tested with different concentrations of *Mentha suaveolens* Ehrh. (Lamiaceae) essential oil (EO) and piperitenone oxide – the main compound of the EO. African green monkey kidney (VERO) cells were incubated with HSV-1 and afterwards treated with *M. suaveolens* EO and piperitenone oxide. The inhibiting concentration 50 % (IC_{50}) values were 5.1 ± 0.48 µg/ml and 1.4 ± 0.07 µg/ml for the EO and piperitenone oxide, respectively. The most reduction of viral replication of HSV-1 was achieved at a concentration of 30 µg/ml of the EO. At concentrations of up to 10 µg/ml the viral replication was nearly obliterated. The EO and piperitenone oxide also showed synergistic effects with acyclovir (Civitelli, et al., 2014). The EO of *Lippia graveolens* Kunth. and its main compound carvacrol were also investigated against several human and animal viruses. It was shown that the EO had inhibitory effects against HHV-1 (human herpes virus 1), ACVR-HHV-1 (acyclovir-resistant HHV-1),BoHV-2 (Bovine herpes virus -2), HRSV (human respiratory syncytal virus) and BVDV (bovine viral diarrhoea virus). Carvacrol was also active against these human and animal viruses except for HHV-1. The effective concentration 50 % (EC_{50}) were higher for carvacrol than for the EO. This may be due to the synergisitc effect of many components in the EO (Pilau, et al., 2011). Lai, et al., (2012) found that thymol and carvacrol had significant anti-viral activities against HSV-1 with an IC_{50} of 7µM. 90% of HSV-1 was inactiviated after the treatment with thymol or carvacrol. Zhu, et al., (2012) found that the EO of *Paederia scandens* Lour. (Rubiaceae) showed good inhibitory effects against HBsAg (Hepatitis B surface antigen) and HBeAg (Hepatitis B e-Antigen). The EOs of tea tree, eucalyptus and thyme and their major monoterpenes were investigated for their antiviral effects on HSV-1 too. The EOs and the monoterpenes were able to reduce the viral infection by >96 % and >80 %, respectively (Astani, et al., 2010).

The EO of *Cinnamomi ramulus* L. (Laureceae) and its main compound cinnamaldehyde were investigated for their anti-influenza virus (A7PR/8/34) activity. Madin-Derby canine kidney cells were infected with influenza. Both the EO and cinnamaldehyde showed virucidal effects on the influenza virus. The IC_{50} values were $1.85*10^{-7}$ and $5.77*10^{-7}$ g/ml. The virucidal effects are related to the activiation of Toll-like receptor-7 (TLR7) signaling pathway and interleukine receptor associated kinase-4 (IRAK-4) (Liu, et al., 2013). Also the EO of *Schizonepeta tenuifolia* Briq. (Lamiaceae) and the EO compounds menthone and pulegone were tested for their anti-influenza activity by Tang, et al., (2012). The EO and pulegone showed significant anti-influenza effects in the chick embryo test, while all three agents showed antiviral effects on infected mice. Ichihashi & Jimbo, (2012) found that patchouli alcohol has antiviral effects on influenza virus A too. Moreover, the EO of *Mosla dianthera* Thunb. (Lamiaceae) was evaluated for its antiviral, anti-influenza activity. Influenza A/PR/8/34 virus (H1N1) infected mice were used for the test. The infected mice were treated with the EO for five successive days at doses of 90-360 mg/kg. The EO treated mice showed significant decrease in lung viral titers, it inhibited pneumonia and reduced the level of interferone-γ (IFN-γ) and interleukine-4 (IL-4). Thus, the EO of *M. dianthera* exhibited potent anti-influenza effects (Wu, et al., 2012b).

Eryngium alpinum L. and *E. amethystinum* L. (Apiaceae) EO were evaluated for their anti-viral activity. It was found that they were able to reduce the infection with mosaic virus, and an associated satellite (Dunkic, et al., 2013). Liu, et al., (2012b) found that the EO of *Elsholtzia densa* Benth. (Lamiaceae) had anti-viral activities. Moreover, the EO of *Lippia citriodora* Paláu, *Lippia alba* (Miller) N. E. Brown (Verbenaceae) and the compounds citral and limonene exhibited antiviral activities against yellow fever virus with IC_{50} values ranging from 4.3 to 25 µg/ml (Gomez, et al., 2013). *L. alba* and *L. citroideae* were also investigated for their virucidal activity against dengue virus (DENV). Both *Lippia* species showed significant virucidal effects on the tested virus with IC_{50} values of 1.4 - 33 µ/ml (*L. alba*) and 1.9 - 33.7 (*L. citroideae*). Among

the different dengue virus strains, *L. citroideae* showed stronger activity against DENV-1, 2 und 3. The EO exhibited lower activity against DENV-4 (Ocazionez, et al., 2010). Furthermore, porcine epidemic diarrea virus (PDEV) infected VERO cells were treated with the EO of *Artemisia dubia* Wall. (Asteraceae). It showed inhibiting effects of the replication of PDEV with an IC_{50} value of 43.7 μ^3/ml (Kim, 2012).

Eight species of Eucalyptus (Myrtaceae) EO were tested for their antiviral activity. To evaluate the antiviral activity, cells and virus were pre-treated with the EO before the cells were infected. The EO of *E. bicostata* and *E. astringens* showed most significant anti-viral effects with IC_{50} values of 0.7-4.8 mg/ml and 8.4 mg/ml, respectiviely. *E.cinera* and *E. maidennii* also showed moderate antiviral activity with IC_{50} values of 102.131 mg/ml and 136.5-233.5 mg/ml (Elissi, et al., 2012).

Orhan, et al., (2012) evaluated the antiviral activity of different Umbelliferae and Lamiaceae plants (*Anethum graveolens* L., *Foeniculum vulgare* Mill., *Mentha piperita* L., *M. spicata* L., *Lavandula officinalis* Chaix ex Villars, *Ocimum basilicum* L., *Origanum onites* L., *O. vulgare* L., *O. munitiflorum* Hausskn., *O. majorana* L., *Rosmarinus officinalis* L., *Salvia officinalis* L., and *Satureja cuneifolia* Ten.) All of the EOs showed significant inhibitory effects on HSV-1(representative for DNA virus) at concentrations ranging from 0.8 to 0.012µg/ml. Against PI-3 (a representative for RNA virus) the EOs exhibited less inhibition activities*. A. graveolens, F. vulgare M. piperita, M. spicata, O. munitiflorum, O. vulgaris*, and *S. cuneifolia* were found to be active against this virus too.

The EO of *Thymus capitiatus* (L.) Hoffmans & Link (Lamiaceae) was tested for its antiviral effects on HSV-1, ECV 11 (Echovirus 11) and ADV (Adenovirus). HSV-1 and ECV 11 were sensitive to the EO when the virus was pre-treated, while ADV was affected after penetration (Salah-Fatnassi, et al., 2010). Garcia, et al., (2010) evaluated the virucidal activities of several aromatic plants of west Argentina. It was found that the EO of *Lantana grisebachii* (Seckt.) var. *grisenbachii* showed good inhibitory effects on HSV-1 and DENV-2 with IC_{50} values

of 21.1 and 26.1 ppm, respectively. The EO of *L. grisenbachii* was also effective against HSV-2 and acyclovir-resistant herpes viruses.

3 Antinociceptive activity

Formalin-induced nociception was significantly inhibited by *Piper aleyreanum* C.DC (Piperaceae) essential oil (EO). At concentrations of 30 to 100 mg/kg the EO inhibited both phases of formalin licking in rats; however, the antinociceptive effects were more distinct in the second phase. Naloxone, a non-selective opioid antagonist, did not reverse the antinociceptive effect of *P. aleyreanum* EO (Lima, et al., 2012). Other authors found similar results for the EOs of Piperaeae family. Pre-treatment with *Pepromia serpens* (Sw.) Loud (Piperaceae) EO (1h before) caused a significant inhibition of acetic-acid-induced abdominal writhes in mice. The effective concentration 50 % (ED_{50}) value was 188.8 mg/kg (Pinheiro, et al., 2011). Jeena, et al., (2014) found that the EO of *Piper nigrum* L. has antinociceptive effects too. The EO significantly reduced the number of abdominal writhes at concentration of 500 and 1000 mg/kg by 47.94 and 46 %, respectively.

Lippia gracilis Schauer (Verbenaceae) EO significantly inhibited acetic-acid-induced writhes in Wistar rats. Concentrations ranging from 50 to 200 mg/kg per oral (p.o.), 1h before treatment with acetic acid, reduced symptoms by 17.4, 31.4 and 42.8 % dose-dependently (Mendes, et al., 2010).

The EO of *Heracleum persicum* Desf. ex Fisch.(Apiaceae) showed analgesic activity in acetic-acid writhes tests and in formalin tests. The EO inhibited the number of acetic acid-induced writhes at concentrations of 50 and 100 mg/kg by 52 % and 65 %. Formalin induced licking was reduced at concentrations of 50 and 100 mg/kg by 12 % and 24 % respectively. (Hajhashemi, et al., 2009) The same author group (2011) also found that *Bunium persicum* (Boiss) B. Fedtsh. (Apiaceae) fruit EO (100-400 µl/kg, p.o.) showed good

antinociceptive activity. The EO significantly reduced acetic acid-induced writhing as well as pain response of formalin tests in both phases. Two Balkan endemic *Laserpitium* species (*Laserpitium zerny* L. and *Laserpitium achridanum L.*) (Apiaceae) were evaluated for their antinociceptive effects in a rat model. Both EOs showed significant anti-nociceptive effects (Popovic, et al., 2014). *Ligusticum porteri* Coulter & Rose (Apiaceae) EO was also found to have significant antinociceptive activity. It showed potent antinociceptive effects in the writhing test. The main compounds, Z-ligustilide and Z-3-butylidenephthalide exhibited antinociceptive effects in the hot plate test and diligustilide showed a potent reduction in pain in both tests (Juarez-Reyes, et al., 2014).

Zingiber zerumbet Smith. (Zingiberaceae) EO was investigated for its antinociceptive properties using the formalin test. The results showed, that *Z. zerumbet* EO had distinctive analgesic activity. Formalin-induced pain and discomfort were reduced by the EO in both phases. Concentrations of 100 mg/kg produced an antnociceptive activity similar to 100 mg/kg acetyl salicylic acid (Zakaria, et al., 2011). *Z. zerumbet* EO was also evaluated for its antinociceptive effects using the acetic acid abdominal writhes test, capsaicin-induced nociception, glutamate-induced nociception and phorbol-12-myristate-13-acetate (PMA)-induced nociception. The EO showed significant reduction of abdominal writhes at doses of 50, 100, 200 and 300 mg/kg with a percentage of 23.02, 53.89, 83.63 and 98.57, respectively. In the capsaicin-induced nociception test, the EO also showed significant inhibition of pain in a dose-dependent manner (Khalid, et al., 2011). Sulaiman, et al., (2010) also found that the EO of *Z. zerumbet* has antinociceptive effects. It significantly increased the latency of paw-removing in the hot plate test. It also produced significant inhibition of acetic acid induced writhing at concentrations of 30, 100 and 300 mg/kg. The effects are the same as those of acetyl salicylic acid (100 mg/kg). Formalin-induced paw-licking was reduced in both phases too. Other species of the Zingiberaceae family showed similar effects. So Liju, et al., (2011) found, that *Curcuma longa* L. (Zingiberaceae) EO

(turmeric oil) showed significant anti-nociceptive activites using the acetic-acid-induced writhing movement test in mice.

Carrageenan and tumour necrosis factor-α (TNF-α) induced mechanical hypernociception in mice. These animals were treated with α-terpineol. Results demonstrated antinociceptive properties. Pre-treatment with α-terpineol at concentrations of 25, 50 and 100 mg/kg intraperitoneal (i.p.) inhibited mechanical hypernociception. Also prostaglandine E_2 ($PGE_{2)}$ and dopamine-induced hypernociception were significantly reduced by α-terpineol at concentrations of 25, 50 and 100 mg/kg (de Oliveira, et al., 2012). As well the antinociceptive effects of α-bisabolol, another monoterpene, were investigated using formalin test and acetic acid induced writhes. In the second phase of formalin-induced paw licking α-bisabolol showed a significant reduction. It also exhibited less writhing induced by acetic acid by 54.68 % and 64.29 % at concentrations of 25 and 50 mg/kg p.o., respectively. The positive control indomethacin (10 mg/kg) showed 48.52 % of writhing reduction (Rocha, et al., 2011). Furthermore, visceral pain was induced by mustard oil. Here too, α-bisabolol significantly reduced nociceptive behaviour (Leite, et al., 2011). Other monoterpens showed similar effects. For example the monoterpene α-phellandrene was evaluated for its antinociceptive effects. In the formalin test, α-phellandrene, at a concentration of 50 mg/kg, showed inhibition effects of both phases. It also reduced carrageenan-induced hyperalgesia at a dose of 50 mg/kg (Lima, et al., 2012). (R)-(+)-Pulegone, was found to have antinociceptive effect too. It showed significant reduction of nociception in both phases of the formalin test and in the hot plate test (de Sousa, et al., 2011). (-)-Linalool, a monoterpene alcohol which is present in many EOs, was evaluated by Batista, et al., (2010) for its antinociceptive effects using a neuropathic pain model. It significantly decreased the paw withdrawal response and so it showed potent antinociceptive effects.

The analgesic effect of *Cymbopogon citratus* Stapf.and *Eucalyptus citroidora* (Hook.) K.D.Hill & L.A.S.Johnson (Myrtaceae) was tested using tail immersion test. The tails of Wistar rats were kept in hot water

(50°C). Animals treated with EOs were able to keep their tails longer in the hot water bath than untreated rats. The results showed that *E. citroidora* EO was more effective than the EO of *C. citratus* (Gbenou, et al., 2013). The EO of *Pimenta pseudocaryophyllus* (Gomes) L. R. Landrum (Myrtaceae) at concentrations of 60, 200 and 600 mg/kg exhibited potent antinociceptive effects in the acetic acid writhing test (de Paula, et al., 2012)

Carvacrol was investigated for its antinociceptive effects using carrageenan-induced mouse paw mechanical hypernociception. At doses of 50 and 100 mg/kg, applicated 30 min before carrageenan injection, carvacrol significantly inhibited the hypernociceptive response. Carvacrol at these doses had similar effects as indomethacin (10 mg/kg) (Guimaraes, et al., 2012b). Furthermore, male mice were pre-treated with carvacrol (i.p.) at doses of 25, 50 and 100 mg/kg. I.p. treatment with carvacrol reduces pain behaviour in both phases of the formalin test. It also had significant antinociceptive effects in the capsaicin and glutamate test at all concentrations (Guimaraes, et al., 2012). Cavalcante, et al., (2012) also found, that carvacrol at doses of 50 and 100 mg/kg showed high reduction of nociception in the acetic acid writhing test and the hot plate test. The antinociceptive effects of carvacrol were not reversible by naloxone or L-arginine.

The EO *of Illicium lanceolatum* A.C. Smith (Illiciaceae) showed distinct antinociceptive properties in acetic acid writhing tests. The EO was able to reduce writhing responses at ratios of 26.6 %, 31.73 % and 35.9 % respectively. The highest ratio was achieved at a concentration of 0.8 g/kg (Liang, et al., 2012).

Many new research results concerning the antinociceptive activity were found within the Lamiaceae family. Tail-flicking tests showed significant acute pain reduction at the treatment of *Nepeta crispa* Willd. (Lamiaceae) EO (100 and 200 mg/kg). In the first phase of the formalin test 30, 100 and 200 mg/kg EO exhibited strong reduction of licking duration as well as it did in the second phase except for 30 mg/kg, which did not show any effect in the second phase of formalin-test.

According to these results, authors suggest that *N. cristpa* EO has central and peripheral antinociceptive effects (Ali, et al., 2012). *Ocimum micranthum* Willd. EO, another species of the Lamiaceae family, was studied for its antinociceptive activity too. The EO (15-100 mg/kg p.o.) showed significant reduction in writhing response and the nociceptive response induced by acetic acid. Licking time, induced by formalin was also significantly reduced (de Pinho, et al., 2012). Moreover, *Ocimum gratissimum* L. (Lamiaceae) EO was tested for its antinociceptive effects in mice. In the hot plate test, the EO was able to increase the latency of paw withdrawal at doses of 40 mg/kg. Eugenol (5 and 100 mg/kg), the main compound of the EO, also showed significant reduction of nociception in the hot plate test. The EO at doses of 40 mg/kg also exhibited reducing of paw licking time in the first and second phase of nociception (Paula-Freire, et al., 2013). Basil EO (*Ocimum basilicum L.* Lamiaceae) was found to have significant antinociceptive effects. The EO was able to decrease acetic-acid induced abdominal writhes by 48-78 %, dose-dependently. In the hot plate test the latency of paw removing was also increased by the EO. In the formalin-licking test the EO showed significant reduction of licking in both phases (Venancio, et al., 2011). *Teucrium stocksianum* Bioss. (Lamiaceae) EO also showed significant antinociceptive effects. The inhibition of writhes was 93 % at a concentration of 80 mg/kg (Shah, et al., 2012). Moreover, the antinociceptive activity of *Hyptis pectinata* (L.) Poit (Lamiaceae) was evaluated using acetic acid, formalin and heat as pain stimuli. The EO at concentrations of 10, 30 and 100 mg/kg demonstrated reduced time, the animals spend licking their formalin injected paw (Raymundo, et al., 2011). Acetic acid-induced writhing tests showed that *Satureja hortensis* L. (Lamiaceae) EO significantly reduced abdominal writhes at concentrations of 100 and 200 µl/kg. The formalin test showed inhibition of licking behaviour only in the chronic phase (Hajhashemi, et al., 2010).

The bark EO of *Vanillosmopsis arborea* Baker (Asteraceae) exhibited potent antinociceptive activities. The topical pre-treatment with the EO at concentrations of 25, 50, 100 and 200 mg/kg decreased the

symptoms of both phases of the formalin test. It also decreased the number of eye-wipes induced by 5 M NaCl solution, topically applied. The oral application of the EO also reduced the number of eye wipes (Inocencio, et al., 2014). Maham, et al., (2014) evaluated the antinociceptive effects of the essential oil of *Aretemisia dracunculus* L. (Asteraceae). It showed significant reduction of pain on both phases of the formalin test by 91.4 % and 83.3 % respectively. Also in the hot plate test the EO showed good analgesic activity. The EO of *Centipeda minima* (L.) A. Braun & Asch. (Asteraceae) was also tested for its anti-nociceptive effects using the hot plate test. The EO showed significant reduction of pain induced by hot plate (Zhang, et al., 2013).

Citronellal is a main compound of the EO of *Cymbopogon winterianus* J. (Poaceae). This agent showed significant antinociceptive activity in carrageenan, TNF-α, PGE_2 or dopamine-induced Swiss mice. Citronellal inhibited mechanical nociception at all doses. The effects of citronellal were even higher than those of L-NAME and glibenclamide (de Santana , et al., 2013). Citronellal was also investigated by Quintans-Junior, et al., (2011). It was found that citronellal showed significant reduction of face rubbing-behaviour induced by capsaicin and glutamate in a dose-dependent manner. Brito, et al., (2013) also found that Citronellol showed significant antinociceptive effects. Swiss mice were pretreated with citronellol at concentrations of 25, 50 and 100 mg/kg i.p. The EO compound showed significant reduction in face rubbing behaviour induced by capsaicin at all doses. The pain was decreased in both phases of nociception.

The EO of *Croton adamantinus* Müll. Arg. (Euphorbiaceae) showed mild antinociceptive activity in the first phase of the formalin licking test and even higher effects than morphine on the second phase of this test at concentrations of 50 and 100 mg/kg. Also, the number of abdominal contortions was decreased by the EO at both doses (Ximens, et al., 2013).

The analgesic effect of *Croton tiglium* L. (Euphorbiaceae) was investigated by Liu, et al., (2011). At doses of 25, 50 and 100 mg/kg the

EO showed significant reduction of acetic acid induced writhing. The results exhibited that the EO had low analgesic effects compared to aspirin. *Citrus lemon* (L.) Burm (Rutaceae) EO showed significant antinociceptive effects in acetic-acid writhing tests and the formalin test. The acetic-acid induced writhing was significantly reduced at EO doses of 50, 100 and 150 mg/kg. Licking response after treatment with formalin was also decreased by the EO in a dose-dependent manner (Campelo, et al., 2011).

4 Anti-inflammatory Activity

In a rat study Mueller, et al., (2013) found that turmeric oil, thyme oil and rosemary oil acted as anti-inflammatory substances. In the trial mild colitis was induced by 4% dextran sulphate sodium (DSS) in 6 weeks old rats. The animals were feed with 1494mg/kg *Curcuma longa* L. (Zingiberaceae) oil (turmeric oil), 618mg/kg *Thymus vulgaris* L. (Lamiaceae) oil or 680mg/kg *Rosmarinus officinalis* L. (Lamiaceae) oil. These essential oils (EO) food additives possess anti-inflammatory properties, because they reduce pro-inflammatory mediators, which are increased after the DSS treatment, like nuclear factor kappa B (NFκB), vascular cell adhesion molecule 1 (VCAM-1), monocyte chemotactic protein-1(MCP-1) and cyclooxygenase 2 (COX2). They also reduce pro-inflammatory adhesions molecules (like VCAM-1 and Clnd3) in non-DSS-treated animals, which leads to an improved gut barrier. Of all three EOs, rosemary oil showed the highest activity (Mueller, et al., 2013). Turmeric Oil was also found to block SCW-induced (peptidoglycan-polysaccharid polymer isolated from *Str. pyogenes*) leucocytosis and the granulomatous inflammatory response that occurs at sites of hepatic SCW deposition. The anti-inflammatory effect of the EO was dose-dependent, and was only present at doses ≥ 28 mg/kg/d. While i.p. (intra peritoneal) doses adjustable in therapeutic height were associated with extremely high mortality oral application of doses at 560

mg/kg/d showed no increased mortality in the test animals. The conclusion was drawn that oral application of turmeric oil had promising anti-inflammatory effects with no toxic risks (Funk, et al., 2010). Moreover, turmeric oil showed significant inhibitory effects in rat paw thickness induced by carrageenan or dextran too. Formalin acute inflammation was also decreased when treated with the EO (Liju, et al., 2011).

Zingiber zerumbet Smith. (Zingiberaceae) at doses of 30, 100 and 300 mg/kg significantly reduced carrageenan-induced paw oedema in rats dose-dependently. The Cotton Pellet-induced Granuloma Test also showed a significant anti-inflammatory activity of *Z. zerumbet* EO in a dose dependent manner (Zakaria, et al., 2011). Furthermore, *Zingiber officinale* Roscoe (Zingiberaceae) was found to have high anti-inflammatory activity. Lipoxygenase (LOX) was inhibited by 50.9 % at a concentration of 0.4 mg/ml. At a dose of 8 mg/ml LOX-inhibition was complete (by 100 %). *Ocimum basilicum* L. (Lamiaceae)*, Eucalyptus camaldunensis* Dehnhardt (Myrtaceae)*, Lippia multifolia* L. (Verbenaceae)*, Hyptis spicigera* Lamarck (Lamiaceae)*, Ageratum conyzoides* L (Asteraceae). and *Ocimum* americanum L. (Lamiaceae) also showed inhibitory effects at a concentration of 8 mg/ml by 98.2 %, 96.4 %, 96.4 %, 75.1 %, 48.3 % and 31.6 %, respectively. These EOs showed no significant inhibitory effects at a concentration of 4 mg/ml (Bayala, et al., 2014).

Cypressus sempervirens L. *var. horizontals*, *Cypressus sempervirens var. pyramidales*, *Juniperus communis* L., *Juniperus excelsa* M. B., *Juniperus foetedissima* Wild., *Juniperus oxycedrus* L. and *Juniperus phoenicea* L. (all Cupressaceae)were evaluated for their potential anti-inflammatory activity in rats. Increased capillary permeability was induced by acetic-acid in mice. *J. oxycedrus ssp.oxycedrus* and *J. phoenicea* were found to be potential anti-inflammatory substances at a dose of 200mg/kg with highest inhibitory values of 33.1% and 27.3% respectively. At a concentration of 100mg/kg both species showed no significant anti-inflammatory activity (Tumen, et al., 2012). The EO of

Juniperus virginiana L. and *Juniperus occidentalis* Hook. also showed anti-inflammatory effects at a concentration of 200 mg/kg using the Whittle method (Tumen, et al., 2013). Moreover, *Juniperus macrocarpa* Sibth. et Sm. EO was found to inhibit the activity of cyclooxygenase-1 (COX1) and LOX-12 as well as aspirin® and quercitin, well known as potent COX-1 and LOX-12 inhibitors (Lesjak, et al., 2014).

Sycygium cumini Skells and *Psidium guajava* L. (Myrtaceae) were found to inhibit effectively the migration of eosinophils and neutrophil stimulated lipopolysaccharids (LPS). Therefore, these EOs were confirmed to be useful for the treatment of inflammatory diseases (Siani, et al., 2013). *Melaleuca alternifolia* Cheel another species of the Myrtaceae family, was found to have potent anti-inflammatory properties. The major compound of the EO is terpinen-4-ol, which exhibits anti-inflammatory activity too. It decreases the production of tumour necrosis factor α (TNF-α), Interleukin 1 (IL-1), IL-8 and prostaglandine E_2 (PGE2), which are potent pro-inflammatory agents (Pazyar & Yaghoobi, 2012). *Cleistocalyx operculatus* (Roxb.) Merr and Perry (Myrtaceae) EO was also investigated for its anti-inflammatory activity. LPS-induced production of TNF-α and IL-1β in RAW 264.7 cells (mouse leukaemic monocyte macrophage cell line) was significantly inhibited by *C. operculatus* EO. Treatment with 10 µg/ml and 20 µg/ml caused 33 % and 45 % inhibition of TNF-α production, respectively. These effects are attributable to the suppression of LPS-induced messenger RNA expression of TNF-α and IL-1β. These results showed that the reduction of pro-inflammatory agents occurs mainly at transcriptional level. EO treatment also decreased LPS-induced NFκB activity in RAW 264.7 cells. The in-vivo tests it exhibited potent anti-inflammatory effects as well. Therapy of inflamed mouse ears, pre-treated with 12-O-tetradecanoylphorbol-13-acetate (TPA) with *C. operculatus* EO completely blocked skin inflammation. 0.1% and 1% EO was more effective than 1% hydrocortisone (Dung, et al., 2009). In vivo tests with carrageenan-induced paw oedema in rats showed that *Myrciaria tenella* (DC.) Berg (Myrtaceae) EO (50 mg/kg) significantly reduced the symptoms like indomethacin (10 mg/kg). In-vitro tests

proved, that *Calycorectes sellowianus* O. Berg and *M. tenella* EO (Myrtaceae) reduced leucocytes migration of the inflamed tissue (Apel, et al., 2010). Furthermore, *Myrtus communis* L. (Myrtaceae) EO exhibited an effective decrease of croton oil-induced ear oedema in rats as well as myeloperoxidase activity. Moreover the oil blocked cotton pellet-induced granuloma and the level of TNF-α and IL-6 in serum (Maxia, et al., 2011). El-Ahmady, et al., (2013) aslo found that the leaf and fruit EO of *Psidium guajaya* L. (Myrtaceae) inhibited the LOX-5 with IC_{50} values of 32.53 and 49.76 µg/ml, respectively.

Linalool, a major compound in several EOs of aromatic plants, was found to have anti-inflammatory activity. Tests showed inhibition of LPS induction of IL-6, TNF-α and NFκB. Also, mitogen-activated protein-(MAP-) kinase pathway was blocked by linalool. The in-vivo study also exhibited significant reduction of IL-6 and TNF-α as well as a significant decrease of inflammatory cells like neutrophils and macrophages. Histological changes in infected lung tissue could be alleviated with linalool treatment (Huo, et al., 2013).

Moreover, many anti-inflammatory effects were found within the Lauraceae family. The EO of *Ocotea quixos* Lam. (Lauraceae) and its main constituent trans-cinnamaldehyde showed promising anti-inflammatory activity. They inhibited NO release from J774 macrophages in a dose dependent manner. The EO also increased the level of cyclic adenosine monophosphate (cAMP) in Forskolin-stimulated SK-N-MC cells. Moreover, *Ocotea* EO (1-10 µg/ml) reduced LPS-induced COX-2 expression, dose-dependently. In-vivo tests showed significant reduction of carrageenan-induced swelling in rat paws. Maximum inhibition (about 20% compared to vehicle treated rats) was achieved with *Ocotea* EO at concentrations of 30 mg/kg and 10 mg/kg of trans-cinnamaldehyde respectively (Ballabeni, et al., 2010). The anti-inflammatory potency of *Neolitsea sericea* (Blume) Koidz.(Lauraceae) leaf oil exhibited excellent dose-dependent inhibitory activities on nitric oxide (NO), PGE_2, TNF-α, IL-1β, and IL-6, which were LPS-induced in RAW 264.7 macrophages. COX-2 and MAP-Kinase

pathway as well as NFκB in association of IκB-α were suppressed by the EO (Yoon, et al., 2010a). *Lindera umbellata* Thunberg (Lauraceae) EO and its main compound linalool were tested for their inhibitory activity on LPS-induced NO production. Cells treated with *L. umbellata* EO and linalool (25, 50 µg/ml) significantly reduced the NO production. The EO also showed decrease of IL-6 mRNA expression. Linalool (50 µg/ml) suppressed TNF-α mRNA expression. Furthermore, NO-Synthetase (iNOS) and COX-2 mRNA expression was diminished (Maeda, et al., 2013). The leaf EO of *Cinnamomum osmophloeum* Kaneh. (Lauraceae) and its main compounds were found to have excellent anti-inflammatory activities. The leaf oil strongly inhibited NO production, with inhibiting concentration 50 % (IC_{50}) ranging from 9.7-15.5 µg/ml (Tung Y.-T. , et al., 2010).

Anti-inflammatory activity of *Zizyphus jujuba* Meikl (Rhamnaceae) seeds EO was investigated. The authors used the TPA-induced skin inflammation model. Topical application of *Z. jujuba* oil (1 % and 10 %) definitely inhibited the increase of ear thickness which was measured to be 0.30±0.02 and 0.35±0.01 mm. Therefore, EO treatment showed improvement of 51 % and 53 %, respectively. Hydrocortisone, the positive control, only caused 39 % of decreased ear thickness (Al-Reza, et al., 2010).

Artemisia fukudo Makino (Asteraceae) EO was evaluated for its anti-inflammatory activity. It exhibited dose-dependent inhibition of the production of NO and PGE2. The results indicate that the inhibitory effects are dependent on the suppression of iNOS and COX-2. The EO also suppressed the production of TNF-α, IL-1β and IL-6. LPS-induced NFκB and IκB-α production was also reduced by *A. fukudo* EO (Yoon, et al., 2010b)

Abies koreana Wilson (Pinaceae) EO was investigated for its anti-inflammatory activity using LPS-induced RAW 264.7 macrophages. The EO of *A. koreana* at doses of 12.5, 25 and 50 µg/ml showed dose-dependent inhibition of LPS-induced NO production. LPS-induced COX-2 activity was also suppressed by the EO and consequently the PGE_2

concentration was reduced. The results exhibited promising anti-inflammatory properties of the EO of *A. koreana* (Yoon, et al., 2009).

Five selected herbs were investigated for their anti-inflammatory activity. *Thymus vulgaris* EO showed stronger inflammatory inhibition than the positive control (tea tree oil, α-bisabolol). In lipoxygenase-5 (LOX-5) inhibition assay *Lindernia anagalis* (Burm.f.) Pennell (Linderniaceae) and *Pelargonium fragrans* Willd. also showed anti-inflammatory activity (Tsai, et al., 2011). *T. vulgaris* EO is rich in thymol and carvacrol. The EO and both constituents were tested for their anti-inflammatory activity using a pleurisy model. *T. vulgaris* EO (250, 500 and 750 mg/kg) reduced inflammatory response. At a concentration of 750 mg/kg the EO also reduced the number of cell migration. Thymol and carvacrol (400 mg/kg) reduced the volume of pleural exudates by 47.3 % and 34.2 % as well as cell migration. Carvacrol also suppressed COX-2. The efficacy of the topical application of thymol and carvacrol was evaluated using croton oil-induced ear oedema. Croton oil induces increased weight of the ears. CVL at doses of 10 mg/ear reduced ear oedema similar to dexamethasone (Fachini-Queiroz, et al., 2012). Carvacrol was found to decrease significantly paw oedema induced by histamine or dextrane. The anti-inflammatory activity only occurred at a concentration of 50 mg/kg (46 % and 35 %). Paw oedema induced by Substance P was reduced by 100 mg/kg carvacrol for 46 %. TPA (12-O-tetradecanoylphorbol acetate) and arachidonic acid induced oedema were also significantly reduced (Silva, et al., 2012). α-Terpineol is a monoterpene and a compound of many EOs. Pretreatment with α-terpineol reduced the number of neutrophils in CG-induced mouse pleurisy. NO production in LPS-induced murine macrophages was also significantly reduced, when treated with α-terpineol (1, 10 and 100 µg/ml) (de Oliveira, et al., 2012). Carvacrol is a phenolic monoterpene and a main compound of EOs of *Origanum* and *Thymus* species. Carrageenan-induced paw oedema were significantly reduced by carvacrol at concentrations of 50 and 100 mg/kg, as did dexamethasone, the positive control. Carvacrol inhibited paw oedema by 49.7 %, 65.3 %, and 76.7 % for 25, 50 and 100 mg/kg, respectively.

Leucocyte migration to mouse pleural cavity, dependent on interpleural carrageenan injection, was also inhibited by carvacrol. Moreover, the production of TNF-α was significantly reduced by carvacrol at doses of 25, 50 and 100 mg/kg. LPS-induced NO production by murine macrophages was inhibited by carvacrol (1, 10 and 100 µg/ml) too (Guimaraes, et al., 2012b). Thyme oil (*T. vulgaris*) also showed strong inhibition of LPS-induced COX-2 promoter activity in a dose dependent manner (Hotta, et al., 2010). Thymol, a compound of the essential oil of *Lippia gracilis* Schauer (Verbenaceae) was evaluated for its anti-inflammatory effects. It was found, that thymol reduced carrageenan-induced paw oedema in rats at a concentration of 100 mg/kg. Furthermore, thymol reduced symptoms of carrageenan-induced peritonitis in rats at concentrations of 10, 30 and 100 mg/kg as well as dexamethasone. The thymol-treated rats showed an improvement in histological analysis of rat paws, for histological changes were limited to the superficial areas (Riella, et al., 2012). Mendes, et al., (2010) also investigated the anti-inflammatory effects of *L. gracilis* EO. They found that concentrations of 200 and 300 mg/kg the EO was able to reduce rat paw oedema induced by carrageenan. *L. gracilis* EO also inhibited leucocyte migration into peritoneal cavern after interperitoneal injection of carrageenan. Croton oil, arachidonic acid, capsaicin, phenol and histamine induced oedema were treated with the EO of *Lippia sidoides* Cham. The EO decreased the formation of the croton oil induced ear oedema at a concentration of 2 mg/ear twice daily for 4 days. Also oedema induced by arachidonic acid was reduced by application of *L. sidoides* for 45 %. (Veras, et al., 2013)

Candida-infected tongues were treated with terpinen-4-ol to evaluate the anti-inflammatory activity of this agent. Terpinen-4-ol is the main constituent of tea tree oil. Tongue treatment with terpinen-4-ol at a concentration of 10 mg/ml significantly reduced signs of inflammation. The addition of terpinen-4-ol to macrophage monolayer, which was cultivated with *Candida albicans,* significantly suppressed the production of TNF-α dose-dependently. IC_{50} of terpinen-4-ol was 800 µg/ml (Ninomiya, et al., 2013).

A collagen-induced arthritis (CIA) model showed anti-inflammatory effects of eugenol. Arthritic mice showed lower clinical scores of CIA when treated with eugenol than treated with the vehicle. Eugenol also reduced leukocyte recruitment to the knee joints of arthritic mice and reduced TNF-α, IFN-γ and transforming growth factor-β (TGF-β) in paw samples of arthritic mice (Grespan, et al., 2012). *Syzygium aromaticum* EO (Clove oil) (Myrtaceae) and its main component eugenol exhibited good anti-inflammatory properties. Clove oil (100 µg/well) inhibited production of IL-1β, IL-6 and IL-10. Moreover, it did not make any difference whether clove oil was administered either before or after LPS-induction. Eugenol also inhibited IL-6 and IL-10 but only for IL-10 it did not matter whether eugenol was administered before or after LPS-induction (Bachiega, et al., 2012). Lemongrass oil was found to suppress LPS-induced COX-2 promotor activity at concentrations of 0.002 and 0.004 % to 20 % and 58 % respectively. Moreover citral, the main compound of lemongrass oil, showed LPS-induced COX-2 mRNA and COX-2 protein suppressing activity. However, the suppressing effect of LPS-induced COX-2 protein was more potent than the suppressing effect on LPS-induced COX-2 mRNA (Katsukawa, et al., 2010). Anethole is the main constituent of star anise EO. It was found to have promising anti-inflammatory effects in LPS-induced acute lung injury in mice. At a concentration of 250 mg/kg anethole decreased the number of inflamed cells, including neutrophils and macrophages. The production of inflammatory mediators (TNF-α, matrix metallopeptidase 9 (MMP-9) and NO) was also reduced by anethole. They also suppressed the activation of NFκB by blocking IκB-α degradation (Kang, et al., 2013). Regarding anethole other authors found similar effects. They are major compounds of the EO of *Illicum verum* Hook. f. (Illicaceae) too. Ear oedema induced by croton oil were used as inflammatory model. Anethole (250 and 400 mg/kg p.o.) significantly reduced the repercussions of topical application of croton oil. Carrageenan-induced pleurisy was also inhibited by anethole. Moreover, the EO compounds decreased the number of leukocytes at -concentrations of - 250 and

500 mg/kg - by 48.78 %. NO levels were also significantly reduced (Domiciano, et al., 2013).

Piper aleyreanum C.DC (Piperaceae) EO showed potent anti-inflammatory activity. The intrapleural injection of carageenan induced acute inflammation which was significantly decreased when the animals were treated with *P. aleyreanum* EO 1h prior. The number of neutrophils and mononuclear cells was reduced at EO concentration of 53.6, 21.7 and 43.5 mg/kg of 54±13 %, 66±10 % and 60±8 % respectively (Lima, et al., 2012). *Pepromia serpens* (Sw.) Loud (Piperaceae) showed significant inhibition of carrageenan-induced paw oedema in rats when applied 1h before injection of carrageenan as well as indomethacin. Also, dextran induced oedema in rat paws were inhibited with treatment of the EO 1h before the dextran injection. Pre-treatment with *P. serpens* EO (188.8 mg/kg p.o.) inhibited carrageenan-induced migration of leucocytes and neutrophils by 58.5 % and 63.1 %. (Pinheiro, et al., 2011). The EO of *Piper nigrum* L. (Piperaceae) was evaluated for its anti-inflammatory effects. Carrageenan-induced abdominal writhes were reduced significantly by 72 % at a concentration of 500 mg/kg. Acute inflammation induced by dextran was also reduced by the EO at concentrations of 100, 500 and 1000 mg/kg by 33.3, 53.3 and 73.4 %, respectively. Chronic inflammation, induced by formalin was even more reduced than acute inflammation (Jeena, et al., 2014).

Pistacia lentiscus L. (Anacardiaceae) EO was evaluated for its anti-inflammatory effects on carageenan-induced rat paw oedema and cotton pellet induced granuloma. The oil significantly reduced the production of TNF-α and IL-6 as well as the cotton pellet-induced granuloma (Maxia, et al., 2010).

The anti-inflammatory effects of *Echinacaea purpurea* L. (Asteraceae) were investigated by using xylene-induced mouse ear oedema, egg-white-induced rat paw oedema and cotton-induced granuloma tissue proliferating in mice. Low, medium and high dose of *E.purpurea* EO showed inhibition of 39.24 %, 47.22 % and 44.79 % in xylene-induced

ear oedema, respectively. The high dose of *E. purpurea* EO also showed significant inhibition of paw oedema (48.51 %) and cotton-induced granuloma (28.52 %). Moreover the pro-inflammatory mediators such as IL-2, IL-6 and TNF-α were reduced in the treated group. (Yu, et al., 2013). *Artemisia capillaris* Thunb. (Asteraceae) EO significantly inhibited the secretion on NO in LPS-stimulated RAW 264.7 macrophages. It also suppressed the production of PGE2 and the expression of COX-2 in these cells. The anti-inflammatory effects may be correlated to the blockade of MAP-Kinase pathway and to the inhibition of NFκB (Cha J. D., et al., 2009). The EO of *Anthemis wiedemanniana* Fisch. & C.A. Meyer (Asteraceae) showed inhibition effects of NO production in RAW 264.7 macrophages. These macrophages were pre-treated with LPS, which induced NO production. At a concentration of 200 µg/ml the EO exhibited an inhibitory effect of 93 %. The IC_{50} value was more significant than the IC_{50} of the reference drug indomethacin (Conforti, et al., 2012). The main compounds of the volatile oil of *Centipeda minima* (L.) A. Braun & Asch. (Asteraceae) showed significant suppressing effects on rat´s paw oedema induced by fresh egg white, and ear oedema induced by xylene (Zhang, et al., 2013).

The EO of *Chamaecyparis obtusa* (Siebold & Zucc.) Endl. (Cupressaceae) showed promising decrease of the production of LPS-induced PGE-2 and peripheral blood mononuclear cells. The expression of TNF-α and COX-2 was also inhibited. These results showed promising anti-inflammatory activity (An, et al., 2013).

Leaf EO of *Cymbopogon winterianus* J (Poaceae) reduced carrageenan-induced neutrophil migration to the peritoneal cavity. The reduction of this inflammatory symptom was dose dependent with 35.5 %, 42.8% and 66.1 % at concentrations of 50, 100 and 200 mg/kg, respectively (Leite, et al., 2012). Anti-inflammatory activity of the EO of *Cymbopogon citratus* Stapf. and *Eucalyptus citroidora* (Hook.) K.D.Hill & L.A.S.Johnson (Myrtaceae) was evaluated. *C. citratus* EO was found to have a reducing effect on formol-induced oedema dose-dependently

(Gbenou, et al., 2013). Myrtol a constituent of eucalyptus EO, was tested for its anti-inflammatory activity on alveolar macrophages from patients with chronic obstructive pulmonary disease (COPD). These cells were pre-cultured with eucalyptus oil and myrtol for 1h. Afterwards they were stimulated with LPS. Myrtol showed 37.3 % reduction of TNFα in a 0.0001 % dilution. It also decreased the quantity of IL-8 and GM-CSF (Granulocyte macrophage colony-stimulating factor*)* by 12.3 % and 35.8 %, respectively (Rantzsch, et al., 2009).

Pterodon polygalaeflorus (Benth) (Fabaceae) EO was investigated for its anti-inflammatory effects with the air pouch model. The EO reduced acute inflammatory symptoms and inhibited lymphocyte proliferation. It also diminished neutrophile migration to the inflamed tissue (Velozo, et al., 2013).

The injection of 1 ml carrageenan into pouches of mice induced increased exudate volume. Pre-treatment with *Hyptis pectinata* (L.) Poit (Lamiaceae) EO significantly reduced these symptoms. Furthermore, *H. pectinata* EO reduced IL-6, TNF, PGE2 and NO concentration in the exudates (Raymundo, et al., 2011). Supercritical fluid extraction of oregano (*Origanum vulgare* L. Lamiaceae) EO (S1 and S2) was also evaluated for its anti-inflammatory properties by using oxidated low density lipoprotein (oxLDL) -activated THP-1 macrophages. These cells showed increased release of cytokine, such as TNF-α, IL-1β, IL-6 and IL-10. Treatment with S1 and S2 showed decrease of all pro-inflammatory cytokines. This happened in a dose-dependent manner. Tests exhibited that the reduced TNF-α production is attributed to the gene expression (Ocana-Fuentes, et al., 2010). The anti-inflammatory properties of *Ocimum americanum* L. (Lamiaceae) EO were investigated using zymosan-induced arthritis. The EO suppressed leukocite migration and reduced paw oedema induced by zymosan. Also IF-γ and TGF-β levels were decreased by the EO (Yamada, et al., 2013). Paw oedema were induced by formalin and treated with *Nepeta crispa* Willd. (Lamiaceae) EO. The paw oedema was significantly reduced by 69 %, 74 % and 43 % at concentration of 30, 100 and 200

mg/kg (Ali, et al., 2012). Different concentrations of *Rosmarinus officinalis* L. (Lamiaceae) EO were tested by in vitro chemotaxis assay and on in-vivo leucozyte migration. In vitro and in vivo tests showed significant reduction of leucozyte migration (de Melo, et al., 2011). The anti-inflammatory effect of the EO of *Nepeta glomerata* Montbret et Aucher ex Bentham (Lamiaceae) was investigated. LPS-induced RAW 264.7 macrophages were treated with different concentrations of the EO. LPS induced NO production of the macrophages was decreased by the EO. The IC_{50} value was 78.1 µg/ml (Rigano, et al., 2011). Neves, et al. (2010) evaluated the anti-inflammatory effects of *Mentha x piperita* L. (Lamiaceae) *Origanum virens* L. (Lamiaceae), *Lavandula luiseri* L. (Lamiaceae) and *Juniperus oxycedrus* L. subsp. oxycedrus (Cupressaceae). Four of these five EO showed reduction of IL-1 induced NO production. The greatest effect was obtained with *J. oxycedrus* EO with inhibition of 80 ± 8 % at a concentration of 0.02 % (V/V).

Distachoselinum tenuifolium (Lag.) Garcia Martin &Silvestre (Apiaceae Umbelliferae) showed inhibition effects in LPS-induced NO production. At concentrations of 0.64 and 1.25 µl/kg the EO reduced NO production after LPS stimulation by 117.7±3.7 % and 125.6±3.2 %, respectively (Tavares, et al., 2010). Oral application of *Heracleum persicum* Desf. ex Fisch. (Apiaceae Umbelliferae) EO at concentrations of 100 and 200 mg/kg reduced carrageenan-induced paw oedema by 33 % and 48 % respectively (Hajhashemi, et al., 2009). *S. hortensis* EO was investigated for its anti-inflammatory activities by using carrageenan-induced paw oedema. The EO (400 µl/kg) significantly inhibited the carrageenan-induced paw oedema (Hajhashemi, et al., 2010). *Bunium persicum* (Boiss) B. Fedtsh. (Apiaceae) fruit EO significantly reduced the inflammatory response of carrageenan-induced oedema. Also croton oil-induced ear oedema was inhibited of *B. persicum* EO (Hajhashemi, et al., 2011). Popovic, et al., (2014) evaluated the anti-inflmmatory and anti-oedematous activities of two Balkan endemic *Laserpitium* L. species (*L. zernyi* and *L. ochridanum*) (Apiaceae). Both EOs significantly reduced the paw oedema at concentrations of 25.50

and 100 mg/kg. The anti-inflammatory activity increased with an increasing dose.

Acute dermatitis was induced by croton oil, arachidonic acid, phenol and capsaicin. The dermatitis was treated with α-bisabolol. The EO compound showed good anti-inflammatory activity (Leite, et al., 2011). (-)-α-Bisabolol is a sesquiterpene alcohol and the main compound of the EO of *Matricaria chamomilla* L. (Asteraceae). It was evaluated for its anti-inflammatory activity using carrageenan-induced mouse paw oedema. α-Bisabolol was able to reduce the paw oedema at concentrations of - 100 or 200 mg/kg - at pre-treatment and so did indomethacin, the positive control. It also had significant reduction effect in oedema induced by dextran. Rat treatment with sesquiterpene alcohol (100 and 200 mg/kg) showed a significant decrease of leucocyte migration on carrageenan-induced peritonitis. The level of TNF-α in the peritoneal fluid was definitely reduced in rats when treated with α-bisabolol (Rocha, et al., 2011).

In vitro tests of the leaves essential oil of *Cedrelopsis grevei* Baill. & Courchet. (Rutaceae) showed good 5-LOX inhibitor activity. IC_{50} values are 21.33±0.5 mg/l, therefore authors concluded good 5-LOX inhibitor properties (Afoulous, et al., 2013). *Citrus sunki* Hort. ex. Tan. and *Fortunella japonica var. margarita* Swingle EO (Rutaceae) were tested for their anti-inflammatory activity. The EOs reduced LPS-induced production of NO in RAW 264.7 cells. These findings indicate that the EOs have anti-inflammatory effects (Yang, et al., 2010).

The topical application of the EO of *Myrica esculenta* Buch. Ham. Ex D. Don. (Myricaceae) exhibited strong suppression of mouse ear oedema, induced by xylene. The anti-inflammatory activity of the EO was found to be 85.3 % at topical application. Diclofenac exposed 87.5 % of inhibition, which is somewhat more than for the EO. Nevertheless *M. esculenta* EO showed potent anti-inflammatory properties (Agnihotri, et al., 2012).

Illicium lanceolatum A. C. Smith EO (Illicaceae) was evaluated for its anti-inflammatory activity using xylene-induced ear oedema test. In a dose-dependent manner the EO of the roots of *I. lanceolatum* at doses of 0.4, 0.6 and 0.8 g/kg significantly reduced the effects of xylene in mouse ears (29.8 %, 30.9 % and 35.3 %). These results are slightly lower than those of dexamethasone (49.1 %) (Liang, et al., 2012). The EO of *Illicium anisatum* L. (Illicaceae) was tested for its anti-inflammatory effect using Raw 264.7 cells. LPS-induced NO production in these cells was significantly decreased in the presence of *I. anisatum* EO. The EO also suppressed the production of PGE2 in LPS-induced cells in a dose-dependent manner. It was found, that the EO interferes with the expression of iNOS and COX-2 mRNA (Kim, et al., 2009)

Limonene was found to decrease MCP-1 (Monocyte chemoattractant protein -1) production in df-HL-60 cells at concentrations greater than 14.68 mmol/L. MCP-1 is one of the C-C chemokines which are spontaneously produced by eosinophile. Diesel exhaust particles (DEPs) -induced MCP-1 production was also reduced by limonene at a concentration of 14.68 mmol/L. Furthermore, the activity of NFκB in relation to the treatment of limonene was significantly decreased. MAP-Kinase pathway was also suppressed by limonene. These tests showed promising anti-inflammatory activity of limonene (Hirota, et al., 2010).

The EO of *Annona sylvatica* A. St.-Hil. (Annonaceae) was evaluated for its anti-inflammatory activity using carrageenan induced paw oedema and CFA (a mixture of oils and water with killed *Mycobacterium tuberculosis*), which induced intense inflammation. The results exhibited inhibition of carrageenan induced paw oedema at doses of 2, 20 and 200 mg/kg for 19 % ±3%, 27 % ± 7 % and 35 % ± 2 %. In the CFA model the EO also showed significant anti-inflammatory activity against persistent inflammation (Formagio, et al., 2013). *Xylopia parviflora* (A. Rich.) Benth. (Annonaceae). EO showed anti-inflammatory effects. The NO-production in LPS-induced RAW264.7 macrophages was significantly decreased by the EO (Woguem, et al., 2014).

Rose geranium (Geraniaceae) EO was evaluated for its anti-inflammatory activity using several in vivo tests. The EO showed significant reduction of carrageenan-induced paw oedema in mice at concentrations of 100, 200 and 400 mg/kg for 30, 38 and 73 % respectively. The effects were not significantly different than those of Diclofenac (50 mg/kg). The formation of croton oil-induced ear oedema in mice was also enhanced using *rose geranium* EO. Histopthology analyses showed that oedematous ear thickness, and substantial inflammatory cell infiltration in the dermis with associated connective tissue disturbance were significantly decreased after using the EO (Boukhatem, et al., 2013).

The seed EO of *Ceiba pentandra* (L.) Gaertn. (Malvaceae) was found to have potent anti-inflammatory activity by (Ravi & Raghava, 2014).

Curcumol is a main compound of the EO of *Curcuma longa* L (Zingiberaceae). The anti-inflammatory effect was investigated using LPS-induced RAW 264.7 macrophages. Curcumol inhibited NO production in LPS-induced RAW 264.7 cells in a dose-dependent manner. iNOS was not affected by The EO component (Chen, et al., 2014).

5 Vasodilatory activity

Pinto, et al., (2009) found that *Alpinia zerumbet* (Pers.) Burtt. et Smith (Zingiberaceae) and its main constituent 1,8-cineole showed vasorelaxant effects. The effects are fully attributed to the integrity of a functional vascular endothelium. The methanolic fraction of essential oil of *Alpinia zerumbet* (Pers.) Burtt. et Smith (MFEOAz) was investigated in in-vitro and in-vivo experiments. MFEOAz at concentrations ranging from 0.1 to 3000 µl/ml reduced contraction in porphyrine-induced aorta rings, extracted from Wistar rats. MFEOAz also significantly reduced $CaCl_2$-induced contraction. To support the in-vitro vasorelaxing properties in-vivo tests were conducted with hypertensive rats. These

tests also showed good antihypertensive properties of MFEOAz (da Cunha, et al., 2013). *A. Zerumbet* fruit oil was also investigated for its vasodilating activity. It was found that the EO had relaxing effects on endothelium-with aortic rings pre-contracted with norepinephrine (1.0 µM) or potassiumchloride (60µM). The vasodilatory effect was stronger on norepinephrine pre-contracted endothelium-with aortic rings than on KCl pre-contracted ones. The relaxing effect on endothelium intact aortic rings was found to be fully related to nitric oxide (NO)/guanylatecyclase-system (Tao, et al., 2013).

The essential oil (EO) of *Citrus bergamia* Risso (bergamot oil) (Rutaceae) was investigated for its vasodilatory activity. Bergamot oil induced relaxation of mouse-aortic rings contracted with 3 µM prostaglandine Fα (PGFα). The effective concentration of 50 % (EC_{50}) was determined to be 0.047 % (v/v). Maximum relaxation was obtained at a concentration of 0.2 % (v/v). Maybe the activation of K^+-channels and the inhibition of Ca^+-influx are involved in the vasorelaxing effect of bergamot oil (Kang, et al., 2012). The EO of *Croton argyrophylloides* Muell. Arg. (Euphorbiaceae) relaxed isolated endothelium-with aortic rings. These were pre-contracted with phenylephrine (Franca-Neto, et al., 2012). Yvon, et al., (2012) evaluated the vasorelaxant effects of six EOs using phenylephrine pre-contracted rat aorta. *Thymus capitatus* L. (Lamiaceae) and *Laurus nobilis* L. (Lauraceae) showed relaxing effects on rat aorta of 96.9 % and 83 % respectively.

Pectis brevipedunculata Sch. Bip. (Asteraceae) EO and its main component citral were investigated for their vasodilating activity in aortic rings of Wistar Kyoto rats. Both induced relaxation of aortic rings, pre-contracted with phenylephrine. EC_{50} of *P. brevipedunculata* for phenylephrine-induced contraction of endothelium-intact and denuded rings were 0.044±0.006 % and 0.093±0.015 % respectively. The EC_{50} of citral were 1.42±0.26 mM and 1.33±0.18 mM, respectively. Also K^+-induced contraction of the aortic rings was inhibited by citral. The vasodilatory effect on KCl-induced contraction of citral was more effective than on phenylephrine-induced contraction. Moreover, citral

alleviates the contractile response of Ca^{++}. Maximal contraction induced by $CaCl_2$ was reduced to 53.38±5.33 % compared to control or completely removed at citral concentration of 0.6 and 6 mM (Lopes Pereira, et al., 2013).

Ocimum gratissimum L (Lamiaceae) EO was determined for its vasorelaxant effects in aortas and mesoteric vascular beds of rats. The EO relaxed aortas pre-contracted by phenylephrine in dependence of concentration. The interaction is completely dependent on endothelial nitric oxide (NO) release in mesoteric vascular beds, and partly related on NO release in the aortas (Pires, et al., 2012).

The EO of *Aniba canelilla* (H. B. K.) Mez (Lauraceae) and its main compound 1-nitro-2-phenylethane (NP) were investigated for their vasodilating activity in an in-vivo study with spontaneously hypertensive rats. The hypotensive and bradycardic effects were significant at concentration of 1 mg/kg. At 5 and 10 mg/kg the effect response to NP, and at 10 and 20 mg/kg to the EO were biphasic. There occurred a first rapid effect 1-1.5 and 1.5-2.5 sec. after injection and a second hypertensive and bradicardic effect after 3.6 and 4-8 sec. respectively. There were no significant differences between the EO and NP detected. The in-vitro study also showed promising vasorelaxant effects of aorta preparations with intact endothelium. All these effects of the EO were attributed to the main compound NP (Interaminense, et al., 2011). A. canellila EO and NP were tested for their vasorelaxant activity on mesenteric arteries. The EO and NP showed relaxing activity in endothelium-containing mesenteric arteries pre-contracted with 75 mM KCl at concentration of 20 µg/ml. The EO and NP also showed significant relaxing activity in phenylephrine and CaCl pre-contracted arteries. All vasodilating effects of the EO an NP were reversible (Interaminense, et al., 2013).

Cymbopogon winterianus J (Poaceae) exihibited hypotension and vasorelaxing effects, which are mainly caused by Ca^{++}-channel blocking. In non-anaesthetized rats an intravenous injection (1, 5, 10 and 20 mg/kg) induced dose-dependent hypotension associated with

tachycardia. A dose of 20 mg/kg induced transitory bradycardia before tachycardia. Moreover, the EO of *C. winterianus* showed vasodilating effects in rat mesenteric artery, which appeared to be mainly related to Ca^{++} -influx (De Menezes, et al., 2010). Citronellol, a monoterpene alcohol and compound of the EOs of *Cymbopogon citratus* Stapf*, C. winterianus*, and *Lippia alba* (Miller) N. E. Brown (Verbenaceae), was found to have hypotensive activity. Bolus injections of citronellol (1, 5, 10 and 20 mg/kg) induced hypotension linked with tachycardia in non-anaesthetized rats. These effects were not dependent on the dose. The in-vitro tests also showed significant vasodilating activity. Citronellol induced relaxation in phenylephrine and KCl pre-contracted rings of mesenteric artery with and without functional endothelium. In endothelium-denuded rings, contracted with $CaCl_2$, Citronellol strongly inhibited vasoconstriction in doses of $1.9 * 10^{-1}$ M, $6.4 * 10^{-1}$ M and 1.9 M (Bastos, et al., 2009).

Thymol and carvacrol two monoterpenic phenol isomers, which are constituents of EOs, induced endothelium-independent relaxation of rat aorta. The effects seem to be related to Ca^{++}-release from the sarcoplasmatic reticulum and/or the Ca^{++}-sensitivity of the smooth muscle cell. Furthermore, it is entirely possible that thymol and carvacrol, at low concentration inhibits the Ca^{++}-influx through the membrane. (Peixoto-Neves, et al., 2010)

The vasorelaxant effect of the EO of *Mentha pulegium* L. (Lamiaceae) was tested in tracheal and bladder smooth muscles isolated from rats. The EO induced relaxation in pre-contracted smooth muscles The relaxing effects are likely to be correlated with the inhibition of Ca^{2+}-entry. The effects are likely to be mediated with the main component pulegone (Soares, et al., 2012).

Trans-caryophyllene, the major compound of many EOs showed significant relaxing effects on the basal tone and on pre-contracted isolated rat trachea. Basal tone was only affected when the endothelium was intact. Trans-caryophyllene demonstrated significant relaxing effects on tracheal muscle, dependent on an induced blocked of Ca^{2+}-

influx through voltage-dependent Ca^{2+}-channels (Pinho-da-Silva, et al., 2012).

6 Cytotoxic Activity

Cedrelopsis grevei Baill. & Courchet. (Rutaceae) essential oil (EO) exhibited cytotoxic effects against MCF-7 cell line (human breast cancer cells) with IC_{50} (inhibitory concentration 50 %) values of 21.5±2 mg/L. The cytotoxic activity of the EO may be attributed to synergistic effects of all terpenes (Afoulous, et al., 2013). Aydin, et al., (2013a) tested the cytotoxic effect of terpinolene, the main compound of many aromatic plants. It showed cytotoxic effects at concentrations of 100, 200 and 400 mg/l in primary rat neurones. In N2a (neuroblastoma) cells terpinolene showed cytotoxic effects already at a concentration of 50 mg/l. The antiproliferative effects of carvone were also tested. High doses of carvone (100,200 and 400 mg/l) showed high cytotoxic effects on N2a cell lines (Aydin, et al., 2013b). The monoterpene myrtenal showed significant anticancer activity. Mice were treated with diethylnitrosamine-phenobarbital, and which furnished an increase of liver weight. Treatment with myrtenal decreased relative liver weight to near normal. α-Fetoprotein and carcinoembryoinic antigen were also significant decreased when treated with myrtenal (Babu, et al., 2012). Eugenol, orally applied 15 days prior, showed significant decrease in the numbers of skin cancer, induced by croton oil (topical application) in Swiss mice. The count of developed tumours in mice was reduced by 42 %. Eugenol was also able to inhibit the proliferation of osteosarcoma cells and human leukaemia cells (Jaganathan & Supriyanto, 2012). Furthermore, *Maleleuca alternifolia* Cheel (tea tree oil) EO and its main compound terpinen-4-ol was found to have anticancer activity on murine tumour cell lines. Inhibiting concentration 50 % (IC_{50}) values were 0.03 % for the EO and 0.02 % for terpinen-4-ol. Both substances

induced cell death by necrosis and low level apoptosis (Greay, et al., 2010).

The EO of *Eugenia caryophyllata* Thunb. (Myrtaceae) and its main compound eugenol were tested against Hela (human cervix carcinoma) cell lines. Eugenol emphasized to be a potent cytotoxic agent against Hela cells (Chang, et al., 2011). *E. caryophyllata* clove EO showed decrease of cell viability at concentrations ranging from 12.5 to 500 µg/ml. The most sensitive cell lines against the EO were MRC-5 (non-cancer human fibroblasts). Among the cancer cell lines murine leukemia macrophages RAW 264.7 were the most vulnerable cells. The IC_{50} value was 18.8 ± 2.4 µg/ml (Kouidhi, et al., 2010).

The EO of *Annona sylvatica* A. St.-Hil. (Annonaceae) was found to have antiproliferative activity. The EO was evaluated for its antiproliferative activity against 9 human tumour cell lines. It was found to have anticancer activity with GI_{50} values (concentration that elicit inhibition by 50 % of the cell growth) of 36.04-45.37 µg/ml. At the highest concentration cytotoxic effects were reached for all cell lines (Formagio, et al., 2013). Furthermore, the leaf EO of *Porcelia macrocarpa* R. E. Fries (Annonaceae) was tested against six cancer cell lines. The EO reduced more than 50 % of viability of the different cancer cells at a concentration of 100 µg/ml. The anticancer effects are possibly due to the compound germacrene D (Da Silva, et al., 2013). The EO of *Xylopia frutesces Aubl*. (Annonaceae) was evaluated for its anticancer activity on OVCAR-8 (ovarian adenocarcinoma), NCI-H358M (bronchoalveolar lung carcinoma) and PC-3M (metastatic prostate carcinoma) human tumour cell lines. The EO exhibited IC_{50} values from 24.6 to 40.0 µg/ml for NCI-H358M and PC-3M cells. In vivo tests also showed significant antitumour activity of the leaf EO. On day 8 the average tumour weight was reduced by 63.2 % in EO-treated mice compared to the control group (Ferraz, et al., 2013).

The EO of *Neolitsea variabillima* (Hayata) Kaneh. & Sasaki (Lauraceae) also showed cytotoxic effects against human oral, liver, lung, colon, melanoma and leukemic cancer cells, as the results of Su, et al., (2013)

showed. They also evaluated the anticancer effects of heartwood EO *of Cunninghamia lanceolata* Lamb. var. konishii (Cupressaceae). The EO showed anticancer activity against human lung, liver and oral cancer cell lines (Su, et al., 2012). Kuramoji, the EO of *Lindera umbellate* Thunberg (Lauraceae) showed inhibitory effects in cell proliferation in in vitro tests. The growth of HL-60 cells, treated with 5 or 50 µg/ml EO for 24 hours was significantly reduced in a dose-dependent manner. It is to suggest, that Kuramoji EO suppressed cell proliferation by induction of apoptosis (Hayato, et al., 2012). Kim, et al., (2009) found that the EO of *Illicium anisatum* L. (Illicaceae) showed low cytotoxic activity against fibroblasts and keratinocytes at a concentration of 100 µl/ml.

Artemisia capillaris Thunb. (Asteraceae) EO was found to have cytotoxic effects on KB cells in a dose-dependent manner. Addition of 0.5 µg/ml EO reduced cell viability by 80 %. The tests also showed that *A. capillaris* EO induced apoptosis at concentrations of 0.5 and 0.5 µg/ml by 24.3 ± 2.8 % and 73.2 ± 2.9 % (Cha, et al., 2009). 20 EOs from herbal plants and citrus fruits were evaluated for their potential antitumour activity. Chamomile (*Matricaria chamomilla,* Asteraceae) showed the strongest inhibitory effect against α and λ mammalian pol (Mammalian DNA polymerase) (Mitoshi, et al., 2012). The leaf and root oils of *Pulicaria jaubertii* E.Gamal-Eldin (Asteraceae) were tested for their antitumour activity against MCF-7 and HEPG-2 (human liver carcinoma cell line) carcinoma cell lines. Both EOs exhibited antitumour effects against both cell lines. The IC_{50} of the leaf oil for MCF-7 cells was 3.8 µg/ml, for HEPG-2 cells IC50 was 5.1 µg/ml. The root oil showed lower activity (Fawzy, et al., 2013). An in vitro cytotoxicity study showed 70.23 % cancer cell (B16F-10 mouse melanoma cells) death when treated with the EO of *Tridax procumbens* L. (Asteraceae). The percentage of tumour nodule formation was also decreased by 71.67 % with the EO when compared to the control group (Manjamalai, et al., 2012). Manjamalai & Grace, (2013) also found that the EO of *Plectranthus amboinicus* (Lour) Spreng (Lamiaceae) had cytotoxic effects on B16F-10 melanoma cells. It showed potent chemotherapeutic and chemoprotective effects over lung metastasis. The EO of *Artemisia*

indica Willd (Asteraceae) was evaluated for its anticancer activity against THP-1 (leukemia), A-549 (Lung), Hep-2, and Caco-2 (coloreactal adenocarcinoma) cancer cell lines. Concentrations of 10 to 100 µg/ml decreased the cell viability of all four cell lines. At a concentration of 100 µg/ml growth inhibition was found to be 95 % (THP-1), 72 % (Hep-2), 82 % (Caco-2), and 78 % (A-549) (Rashid, et al., 2013).

The EO of aerial parts of *Artemisia herba-alba* Asso. (Asteraceae) exhibited significant anti-proliferative effects on CEM (acute lymphocytic leukaemia) cancer cells. The cytotoxic activity started at very low doses (less than 0.5 µg/ml). At a high concentration (50 µg/ml) the cell viability was decreased by 80 %. The IC_{50} value was 3 µg/ml (Tilaoui, et al., 2011).

β-elemene are natural sesquiterpene isolated from the EO of *Curcuma aromatic* Salisb. (Zingiberaceae). They showed antiproliferative effects on several cell lines. The results of in vitro tests exhibited growth inhibition of laryngeal cancer cells. Hep-2-cells were transplanted into nude mice for in vivo tests. β-elemene were also able to inhibit the growth of those induced tumours. The inhibitory rate of β-elemene (40 µg/ml) was 73.7 ± 4.4 %. The antiproliferative effect was found to be related to the cell cycle arrest, the induction of apoptosis, and the inhibition of metastasis (Dai, et al., 2013).

Misharina, et al., (2013) found, that the EO *Origanum vulgare* L. (Lamiaceae) showed significant anticancer activity in in vivo experiments. Engraftment and development of the tumours in F1 DBA C57 black hybrid mice were significantly decreased. The EO of *Marrubium vulgare* L. (Lamiaceae) exhibited significant anticancer activity against HeLa cell lines. Different concentrations (3.91-3000 µg/ml) of *M. vulgare* EO were used. Concentrations up to 250 µg/ml EO showed deletion by 27 %, at higher concentrations (up to 500 µg/ml) all HeLa cells were destroyed. The *M. vulgare* EO showed an IC_{50} value of 0.258 µg/ml (Zarai, et al., 2011). *Salvia officinalis* L. (Lamiaceae) EO was tested for its anticancer activity against oral epithelial cell

carcinoma cell line (UMSCC1). Cell viability was decreased at a concentration of 135 µg/ml to 3 %. IC_{50} value was 135 µg/ml (Sertel, et al., 2011a). *Thymus vulgaris* also showed cytotoxic effects against UMSCC1 cell line with an IC_{50} value of 369.55 µg/ml (Sertel, et al., 2011c). The main compound of the EO of *Nepeta sibirica* L. (Lamiaceae) was found to be nepatalactone. These agents showed cytotoxic activities against HL60 (melanoma) and Kato III (stomach carcinoma) cell lines (Tsuruoka, et al., 2012). Two different EO of *Hyptis spicigera* Lam (Lamiaceae) showed cytotoxic effect against MCF-7 cell line. IC_{50} values were 170 and 84 µg/ml. The cytotoxic effect is based on the compounds of the EO (Bogninou-Agbidinoukoun, et al., 2013).

Xylopia laevigata (Mart.) R. E. Fries (Annonaceae) EO was tested for its anticancer activity in in vitro and in vivo tests. The IC_{50} values were ranging from 14.4 to 31.6 µg/ml in SF-295 (glioblastoma) and OVCAR-8 cell lines. The EO was also cytotoxic to normal cells. In vivo tests were performed with mice, which were transplanted with sarcoma180 cells. These mice were treated with the EO in 5 % DMSO intraperitoneally once a day for 7 days. On day 8, the tumour growth inhibition rates were 37.3-42.5 % (Quintans, et al., 2013).

Pinus desiflora Sieb. et Zucc. (Pinaceae) EO inhibited proliferation and induced apoptosis in YD-8 cells (human oral squamous carcinoma). Cell proliferation was inhibited by 30 % and 60 % at concentrations of 40 and 60 µg/ml EO. The EO reduced cancer cells by 70 % when treated with 60 µg/ml EO. Apoptosis was induced by activation of caspase-9 (Jo, et al., 2012). Soeur, et al., (2011) found that *Aniba rosaeodora* Ducke (Lauraceae) had cytotoxic effects against A431 (human epidermoid carcinoma cell line) and on HaCaT (human keratinocytes) cells. At a concentration up to 400 nl/ml the EO showed significant reduction of cell viability of these cell lines. The cytotoxic activity is due to induction of caspase-dependent apoptosis in the above mentioned cell lines. Non-small cell lung cancer cells were treated with the EO of *L. cubeba*. The vapour of the EO induced apoptosis in the

cancer cells. Cell death was caused through induction of caspase-9 (Seal, et al.). *Boswellia sacra* (Burseraceae) EO was found to have anti-tumour activity against human breast cancer cells. Cell viability in all tested cancer cells was decreased, dependent on the hydrodistillation temperatures of the EOs. MCF-10-2A (immortalized normal breast epithelial cells) were insensitive to the EOs. Therefore, the EOs induces tumour cell-specific death. *B. sacra* EO induced apoptosis in dependence on activation of caspase-8 and caspase-9 (Suhail, et al., 2011). KB cells were treated with the EO of *Cryptomeria japonica* D. Don (Cupressaceae). Cell viability was significantly inhibited when treated with the EO. The treatment with the EO arrested cells in gap-0 (G0) phase, and proliferation was impossible. The EO also activates caspase-8 and induces apoptosis (Cha & Kim, 2012). De Martino, et al., (2011) found that the EO of *Verbena officinalis* L. (Verbenaceae) was able to induce apoptosis in CLL (chronic lymphocytic leukaemia) cells, dependent on the activation of caspase-3. The EO of *Kadsura longipedunculata* Finet & Gagnep. (Schisandraceae) exhibited moderate cytotoxic activity against MIA PaCa-2, HepG2 and SW-480 cell lines with IC_{50} values of 133.53, 136.96 and 136.62 µg/ml, respectively. Cytotoxic activity may be due to the activation of caspase-3 and caspase-7 (Mulyaningsih, et al., 2010)

Lippia gracilis Schauer (Verbenaceae) EO was tested for its in vitro cytotoxic effects against HepG2, K562 (human chronic myelocytic leukemia) and B16-F10 (mouse melanoma) cell lines. These cell lines were treated with different concentrations of the EO for 72h. The major constituents (thymol, p-cymene, γ-terpinene, and myrcene) were tested against the cell lines. The EO exhibited IC_{50} values ranging from 4.93 to 22.92 µg/ml for HepG2 and K562 cells. The compound myrcene was the most cytotoxic agent among the compounds. IC_{50} values ranging from 9.23 to 12.2 µg/ml for HepG2 and B16-F10 cell lines. P-cymene and γ-terpinene only showed cytotoxic effects on B16-F10. Due to these results it can be concluded that the EO of *L. gracilis* is a potent cytotoxic agent (Ferraz, et al., 2013). Other different EOs of Verbenaceae and Asteraceae family were tested for their cytotoxic

activity. *Achillea ligustica* All. (Asteraceae) displayed cytotoxic activity against the B16-F1 cell line, *Ambrosia arborescens* Mill. against Hela. *L. alba* and *L. micromera* Schauer (Verbenaceae) also showed cytotoxic effects on Hela cells (Zapata, et al., 2014). The EO of *Cunninghamia lanceolata* var. konishii (Lamb.) Hook. (Cupressaceae) showed potent cytotoxic effects on human lung, liver and oral cancer cells. The active agent seemed to be cedrol (Su, et al., 2012). The EOs of *Erigeron acris* L. and *E. annuus* (l.) Pers (Asteraceae) were investigated for their anticancer activity against cultured fibroblasts, MCF-7, MDA-MBA-231, endometrial adenocarcinoma (Ishikawa) and colon adenocarcinoma (DLD-1) cells. The EO of *E. acris* showed strong activites on MCF-7 cell line, with an IC_{50} value of 14.5 µg/ml. The EOs had no effects on non-cancer cells (Nazaruk, et al., 2010).

Xylopia laevigata L. (Apiaceae) EO exhibited potent antiproliferative effects against U251 (glioma, CNS), UACC-62 (melanoma), MCF-7 (mamma), NCI-ADR/RES (ovarian-resistant), 786.0 (kidney), NCI-H460 (lung, no small cells), PC-3 (prostate), OVCAR-3 (ovarian), HT-29 (colon) and VERO (african green monkey kidney) cell lines in in vitro tests with total growth inhibition (TGI) of 4.03-36.71 µg/ml. UACC-62, NCI-ADR/RES and NCI-H460 were the most sensitive cells against the EO with TGI lower than 10 µg/ml (Costa, et al., 2013).

The EO mandarin peel (*Citrus reticutata* Blanco Rutaceae) and its main compound, limonene, were tested against A549 and HepG2 cell lines. Both agents showed dose-dependent growth inhibitory effects. The IC_{50} values of limonene were 0.150 µl/ml in HepG2 cells and 0.098 µl/ml in A549 cells. For the mandarin peel oil the IC_{50} values were 0.063 µl/ml and 0.036 µl/ml, respectively (Manassero, et al., 2013).

Costa, et al., (2013) found that the EO of *Annona pickelii* (Diels) H. Rainer and *Annona salzmannii* A. DC (Annonaceae) exhibited potent antitumour effects on U251 (glioma, CNS), UACC-62 (melanoma), MCF-7, NCI-H460 (lung, non-small cells), OVCAR-03 (ovarian), PC-3 (prostate), HT-29 (colon), 786-0 (kidney), K562 (leukaemia) and VERO

(non-cancer cell-line) human tumour cell lines. TGI was lower than 100 µg/ml.

The EO of *Solanum erianthum* D. Don and *Solanum macranthum* Dunal (Solanaceae) were tested for their in vitro cytotoxic effects. *S. erianthum* showed inhibitory effects against Hs 578T (human breast ductal carcinoma) cells and PC-3 (human prostate carcinoma) cells. Fruit oil of *S. macranthum* exhibited anticancer activity against Hs 578T cells by 78 % (Essien, et al., 2012).

The EOs of *Zanthoxylum xanthoxyloides* Lam. and *Zanthoxylum leprieurii* Guill. & Perr (Rutaceae) were evaluated for the growth inhibiting activity on four different human cancer cell lines. Both EOs showed potent against T98G (human glioblastoma), MDA-MB231 (breast adenocarcinoma), A375 (melanoma) and HCT116 (colon carcinoma) cell lines, but the EO of *Z. xanthoxyloides* had stronger growth inhibitory effects than *Z. leprieurii*. The highest activity was achieved on the MDA-MB231cells with IC_{50} values of 18.2 ± 1.5 µg/ml and 76.0 ± 11.1 µg/ml for *Z. xanthoxyloides* and *Z. leprieurii* respectively (Fogang, et al., 2012).

Origanum marjoram L. and *O. vulgare* L. (Lamiaceae) EOs were evaluated for their cytotoxic activity on two human cancer cell lines (MCF-7 and LNCaP) and one fibroblast cell line (NIH-3T3). The EO decreased the cell viability ranging from 79 % to 88 % at a concentration of 0.5 µg/ml. The EO of *O. marjoram* showed notable stronger activity than the EO of *O. vulgare* (Hussain, et al., 2011). *Rosmarinus officinalis* L. EO was tested against MCF-7 and NIH-3T3 (mouse embryonic fibroblasts) cells. The EO inhibited the cell viability by 81-89 % at a concentration of 500 µg/ml. The IC_{50} values were 190.1 and 180.9 µg/ml for MCF-7 and NIH-3T3 cell lines, respectively (Hussain, et al., 2010). *Thymus caespititius* Hoffmanns. & Link (Lamiaceae) EOs was tested for its cytotoxic effects on the cell line ACC201 (adenocarcinoma gastric cells). The cell viability was decreased to 45 %, 30 minutes after the treatment with the EO. At the end of the first hour cell viability was recovered to 65 % at a

concentration of 0.08 mg/ml. Higher concentrations (0.5 and 1.0 mg/ml) were more harmful to the tumour cells. The cell viability decreased to 30 ± 0.05 and 20 ± 0.05 % respectively (Dandlen, et al., 2011).

Different pancreatic cancer cell lines (KLM1, KP4, Panc1, MIA Paca2) and pancreatic epithelial cells (ACBRI515) were treated with 0-250 µM α-bisabolol, a compound of many EOs. α-Bisabolol significantly suppressed the proliferation of KLM1 and KP4 cells at a concentration of 5 µM. To suppress the proliferation of Panc1 and MIA Paca2 cells a higher concentration (6.25 µM) was needed. It was found that α-bisabolol induced apoptosis in consequence of Akt (serin/threonine-specific protein kinase) activation (Seki, et al., 2011).

Murraya koenigii (L.) Spreng (Rutaceae) was evaluated for its in vitro cytotoxic effects against MCF-7, P388 (murine leukemia) and Hela cells. The results showed, that both, the EO and its main compound carbazole alkaloids have significant anti-proliferative effects on all three tested cell lines in a dose- and time-dependent manner (Nagappan, et al., 2011).

The cytotoxic effects of the EOs of *M. communis* and *Eugenia supraaxillaris* Spreng. (Myrtaceae) were evaluated. Both EO samples exhibited strong cytotoxic activity against cervices, colon, larynx, liver and breast cancer cell lines. The activity may be attributed to the presence of limonene, cineole eugenol and methyl eugenol as compounds of the EOs. (Aboutabl, et al., 2011). *Myrcia laruotteana* Camb. (Myrtaceae) EO was tested against U251, UACC-62 (melanoma), MCF-7, NCI-ADR/RES, 786-0 (kidney), NCI-H460, PC-3, OVCAR-3, HT-29, K562 and VERO cells. The EO showed anti-proliferative effects on all tested cancer cell lines, accept for NCI-ADR/RES. TGI was ranging from 20.46 to 88.31 µg/ml. The most sensitive cell lines against *M. laruotteana* EO were U251, 786-0, UACC-62 and PC-3, with TGI lower than 30 µg/ml. The EO also exhibited toxicity against VERO cells (Stefanello, et al., 2011).

Ceratonia siliqua L. (Fabaceae) EO was tested for its cytotoxic effects on Hela, MCF-7 and HUVEC (human umbilical vein endothelial) cells using the MTT test. The EO exhibited, dose dependently, growth inhibition effects on all tested cell lines, but inhibition was significantly stronger in Hela cells than in MCF-7 cells. It also showed lower cytotoxic activity against normal human cells (HUVEC) (Hsouna, et al., 2011).

Patharakorn, et al., (2010) found that the leaf EO of *Morus rotunbiloba* Koidz exhibited cytotoxic activity against Hep2 and SW620 cell lines. The EO showed no toxic effects on VERO cells at concentrations of 0.1-100 µg/ml.

The EO of four different plants grown in Benin (*Ozoroa insignis* Delile, Anacardiaceae; *Pentadesma butyraceae* Sabine, Clusiaceae; *Siphonochilus aethiopicus* (Schweinf.) B. L. Burtt, Zingiberaceae; and *Xylopia aethiopica* (Dunal) A. Rich., Annonaceae) were evaluated for their cytotoxic effects. All four EOs inhibited the proliferation of breast cancer cells. 70 % of all cancer cells were inhibited at the highest test concentration of *P. butyraceae* EO. The IC_{50} value was 133.5 ± 2.6 µg/ml. *S. aethiopicus* at a concentration of 178.0 µg/ml also displayed anti-proliferative effects on MCF-7 cell lines. The IC_{50} values for *X. aethiopica* EO was 127.9 ± 28.8 µg/ml, for *O. insignis* EO the IC_{50} value was >327.6µg/ml. Due to these results, all four EOs, except for *O. insignis*, showed potent cytotoxic activities (Noudogbessi, et al., 2013). The EO of *Casearia lasiophylla* Eichler (Salicaceae) exhibited antiproliferative activity on U251 (glioma), UACC-62 (melanoma), MCF-7, NCI-ADR/RES (ovarian- resistant), PC-3, OVCAR-3, HT-29, K562 and VERO cell lines. The most sensitive cell lines were UACC-62 (TGI: 7.30 µg/ml) and K562 (TGI: 7.56 µg/ml). The cytotoxic effect is possibly due to the attendance of germacrene D, (E)-caryophyllene and α-cardinol in the EO (Salvador, et al., 2011). Flower EO of *Convolvulus althaeoides* L. (Concolvulaceae) exhibited significant cytotoxic effects against human breast cancer cells. The cytotoxic effects of the EO may

be due to the synergistic effects of the active compounds (α-humolene, β-caryophyllene and germacrene D) (Hassine, et al., 2014).

Patchouli alcohol is a main compound of the EO of *Pogostemon cablin* (Blanco) Benth (Lamiaceae). The Treatment with 50, 75 and 100 µM patchuli alcohol reduced the proliferation of HCT116 cells by 22 %, 35 % and 56 % at 24h. The cell proliferation of MCF-7 cells was reduced by 24 % and 59 % at concentrations of 75 and 100µM patchouli alcohol at 24h. The anti-proliferative effects may be due to the induction of apoptosis (Jeong, et al., 2013).

Psidium guajava L. (Myrtaceae) EO of fruits and leaves were tested against HepG2 and MCF-7 cell lines. IC_{50} values of leaf EO were ranging from 130.69 to 351 µg/ml, IC_{50} values of fruit EO were ranging from 196.45 to 544.38 µg/ml. The cytotoxic effect against MCF-7 cells was much lower than against HepG2 cells. The EO concentration used was 0.11 % (El-Ahmady, et al., 2013).

The cytotoxic effects of *Guatteria pogonopus* Maritus (Annonaceae) was evaluated by Fontes, et al., (2013). The used cell lines were OVCAR-8, NCI-H358M and PC-3M. The EO showed cytotoxic effects against all three cell lines. The most sensitive cells were OVCAR-8 cells, the lowest cytotoxic effects were reached on NCI-H358M. The in vivo antitumour activity was trested on mice, transplanted with sarcoma180 cells. The EO exhibited an growth inhibition of 25.3 % and 42.6 % at concentrations of 50 and 100 mg/kg/d.

Marigold (*Tegetes minuta* L.) and basil (*O.basilicum*) (Lamiaceae) EO showed in vitro cytotoxic effects at concentrations of 25 to 200 µg/ml. Both EOs reduced the cell viabilityof HL-60 and NB4 (human leukaemia cell line) cells. 82.33 % of cell death of HL-60 cells was reached at a concentration of 200 µg/ml basil oil. The highest rate of cell death on NB4 cells (81.87 %) was reached with marigold oil at a concentration of 200 µg/ml. Both EOs showed no cytotoxic effects in the in vivo tests (Mahmoud, 2013).

Vepris macrophylla (Baker) I. Verd. (Rutaceae) EO was tested for its anticancer effects by Maggi, et al., (2013). The EO showed inhibitory effects on tumour cell growth on T98G (human glioblastoma), MDA-MB-231, A375 and HCT116 cell lines. The highest activity of the EO was reached against MDA-MB-231 and HCT116 cell lines .The IC_{50} values for these two cell lines were 3.14 ±0.21 and 3.21 ± 0.22 mg/ml. The IC50 value for T98G was 28.4 ± 2.2 mg/ml. These cells were the most resistant against the EO.

Abietane, a new type of natural diterpene, was found in the EO of *Tetradenia riparia* (Hochstetter) Codd. (Lamiaceae). The EO and the diterpene were tested against their cytotoxic activity. The EO and its compounds (abietane) showed prominent anticancer activity against SF-295 (tumoral) cell line by 78.06 % and 94.80 %, respecitvely. Inhibitory effects for HCT-8 cells were 85.00 % and 86.54 %. MDA-MB-435 cells were inhibited by 59.48 % and 45.43 %. These results indicate that the new found agent exhibits promising anticancer activities (Gazim, et al., 2014).

T. serpyllum, T. algeriensis Boiss. And Reut and *T. vulgaris* EO were tested against MCF-7, NCI-H460, HCT-15, Hela and HepG2 cells. T. serpyllum showed the most potent cytotoxic activity against the tested cell lines. The GI50 values were ranging from 7.02 to 52.69 µg/ml. All three EOs exhibited no toxicity against non-cancer cells. MCF-7 cells were the most sensitive cells human cancer cells (Nicolic, et al., 2014).

The EO of *Monarda citriodora* Cerv. ex Lag. (Lamiacaeae) showed chemotherapeutic potential in HL-60 cell lines. It induces apoptosis and disrupted the PI3K/AKT/mTOR signalling cascade. The EO and its main compound thymol also inhibited the cell proliferation of MCF-7, PC-3, A-549 and MDA-MB-231 cells (Pathania, et al., 2013). *Thymus citriodorus* (Pers.) Schreb. ex Schweigg. & Körte (Lamiaceae) showed toxic effects on HepG2 cells. It induced apoptosis associated to the expression of NFκB65. The IC_{50} value was 0.34 % (Wu, et al., 2013).

Lindera strychnifolia (Sieb. And Zucc.) (Lauraceae) leaf EO was investigated for its cytotoxic effects on eight human cancer cell lines. The anticancer activity against Eca-109 (human esophageal carcinoma), HepG2, MDA-MB-231, PC-3 and SGC-7901 (human gastric carcinoma) of the EO was more significant than those of cisplatin. HepG2 was the most sensitive cell line of the leaf EO. It induced apoptosis in the tumour cells (Yan, et al., 2013).

Bou, et al., (2013) evaluated the cytotoxic activity of the EO of *Casearia sylvestris* L. (Salicaceae). It exhibited anti-tumour effects on all tested cancer cells. With IC50 values ranging from12 to 42 µg/ml. The main compound α-Zingiberene showed cytotoxic effects against Hela, U-87 (glioblastome), Siha (uterus carcinoma)and HL60 cell lines.

Further research results concerning the cytotoxic effects of EOs are summarized in Table 1.

Table1:

name of plant and family	sensitive cell line	reference
Eucalyptus benthamii Maiden et Cambage (Myrtaceae)	Jurkat (T leucaemia cells) J774A (murine macrophage tumour) HeLa (Cervical cancer)	Döll-Boscardin, et al., 2012
myrrh (*Commiphora myrrha* Engl. Burseraceae) and frankincense (*Bowellia carterii* and *Commiphora pyracatoides* Engl. Burseraceae)	MCF-7(human breast cancer), HS-1 (human skin)	Chen, et al., 2013a
Mysterica fragrans Houttyn (Mystericaceae)	Human colon adenocarcinoma	Piras, et al., 2012
Rosmarinus officinalis L. (Lamiaceae)	Human ovarian cancer cell lines (SK-OV-3 and HO-8910) and human hepatocellular liver carcinoma cell line (Bel-7402)	Wang, et al., 2012b
Ocimum basilicum L. (Lamiaceae)	HeLa (human cervical cancer cell line), Hep-2 (human laryngeal epithelial carcinoma cells) and NIH 3T3 (mouse embryonic fibroblasts)	Kathirvel & Ravi, 2012
Melaleuca armillaris (Sol Ex Gateau) Sm (Myrtaceae)	MCF7	Chabir, et al., 2011
Levisticum officinale L. (Apiaceae)	UMSCC1.	Sertel, et al., 2011b
Genista tinctoria L. (Leguminosae), Genista sessilifolia DC	Malignant melanoma cells	Rigano, et al., 2010
Schinus molle L. and *Schinus terebinthifolius* Raddi (Anacardiaceae)	MCF-7	Bendaoud, et al., 2010
Litsea cubeba (lour.) pers.	Human lung, liver and oral cancer cells	Ho, et al., 2010

Drucosia anethifolia Boiss. and *Drucosia flabellifolia* Boiss. (Apiaceae)	K562, LS180 (human colon adenocarcinoma) and MCF-7	Shahabipour, et al., 2013
Citrus limettoides Tan. (Rutaceae)	SW480 cells	Jayaprakasha, et al., 2013
Smyrnium olusatrum L. (Apiaceae)	T98G (human glioblastoma multiforme), MDA-MB 231 (human breast adenocarcinoma) and HCT116 (human colon carcinoma)	Quassinti, et al., 2013
The anticancer activity of *Angelica acutiloba* Sieb. & Zucc. (Apiaceae)	HeLa and MCF-7	Roh, et al., 2012
The EO of *Daucus carota* Linn. (Apiaceae)	HuH7 (hepatocellular carcinoma), NCI-H446 (human lung cancer)	Li, et al., 2012a
Pterodon emarginatus Vogel (Fabaceae)	C6 (rat glioma), MeWo (human melanoma), CT26-WT (mouse colon carcinoma), MDA-MB 231 (human breast cancer), A549 (human lung carcinoma), B16-F1 (mouse melanoma), CHO-K1 (hamster ovary cell) and BHK-21 (normal hamster kidney fibroblasts)	Dutra, et al., 2012
Acanthopanax leucorrhizus (Oliv.) Harm (Araliaceae)	Hela, A-549, Bel-7402 (Liver carcinoma) and Hep G2	Hu, et al., 2012
Myrothamnus moschatus (Baillon) Niedenzu (Myrothamnaceae)	Four human glioblastoma cell lines (T98G, U-87 MG, GL15, and U251) and one human breast cancer cell line (MDA-MB 231)	Nicoletti, et al., 2012
Citrus aurantium L. (Rutaceae) peel	Colorectal cell line (Lim1863)	Fadi, et al., 2012
C. citratus EO	Human colorectal (HCT-116), MCF-7	Piaru, et al., 2012a
M. fragrans and *Morinda citrifolia* L. (Rubiaceae)	HCT-116 and MCF-7	Piaru, et al., 2012b

Cleidion javanicum Bl. (Euphorbiaceae) EO	KB-Oral Cavity Cancer, MCF-7 and H187-small Cell Lung Cancer.	(Sanseera, et al., 2012
Satureja sahendica Bornm. (Lamiaceae)	MCF-7, Vero, SW480 (human colon adenocarcinoma) and JET 3 (choriocarcinoma cell)	(Yousefzadi, et al., 2012
Fortunella margarita Swingle (Rutaceae)	LNCaP cell (prostate cancer cells	Jayaprakasha, et al., 2012
Pinus wallichiana P. strobus (Pinaceae)	THP-1, A-549, HEP-2, PC-3 (prostate cancer cells), and IGR-OV-1 (ovarian carcinoma)	(Dar, et al., 2012
Cinnamomum longepaniculatum N. Chao ex H. W. Li leave EO	BEL-7402 (hepatocellular carcinoma)	Ye, et al., 2012
Micromeria fruticosa L. Druce subsp. serpyllifolia	HCT (human colon tumour) and MCF-7 cells.	Shehab & Abu-Gharbieh, 2012
M. spicata EO	HeLa	Liu, et al., 2012a
Senecio leucanthemifolius Poiret (Asteraceae)	COR-L23 (large cell carcinoma) Caco-2, C32 (amelanotic melanoma), HepG-2 and MRC-5 (human fetal lung).	(Ouchbani, et al., 2011
A. wiedemanniana EO	COR-L23 and C23 cell	Conforti, et al., 2012
Anoectochilus roxburghii (Wall.) Lindl. (Orchidaceae)	NCI-H446 (human lung cancer)	(Chen, et al., 2012
Chromolaena odorata (L.) R.M. King & H. Rob (Asteraceae)	Hela, Hep-2 and NIH 3T3 (mouse embryonic fibroblasts)	Prabhu, et al., 2011
Euphorbia macrorrhiza C. A. Mey (Euphorbiaceae)	Caco-2 cell line	Lin, et al., 2012
Ligusticum chuanxiong Hort. (Umbelliferae)	MCF-7, Hela and SK-Hep-1 (liver adenocarcinoma)	Sim & Shin, 2011
Zingiber officinale Roscoe (Zingiberaceae)	HO-8910 and Bel-7402	Wang, et al., 2012a

Hypericum hircinum L. subsp. majus (Aiton) N. Robson	T98G (human glioblastoma), PC3 (human prostatic adenocarcinoma), A431 (human squamous carcinoma) and B16-F1 cell lines.	Quassinti, et al., 2013
Pulicaria undulata Gamal Ed Din (Asteraceae)	MCF-7	Awadh, et al., 2012
Solidago canadensis L. (Asteraceae)	Hela, PLC (human liver carcinoma) and SMMC-7721 (human hepatocellular carcinoma)	Li, et al., 2012b
Capparis spinosa L. (Capparaceae)	HT-29 cancer cells	Kulisic-Bilusic, et al., 2012
Helichrysum gymnocephalum (DC.) Humb. (Asteraceae)	MCF-7	Afoulous, et al., 2011
Cyperus kyllingia Endl. (Cyperaceae)	NCI-H187	Khamsan, et al., 2011
A. campestris	HT-29	(Akrout, et al., 2011
Lycopus lucidus Turcz. var. hirtus Regel (Lamiaceae)	Bel-7402, Hep-G2, MDA-MB-435S and ZR-75-30	Yu, et al., (2011)
Mangifera indica var. coquinho	K562, NCI-ADR/RES, OVCAR-3, NCI-H460, 786-0 and UACC-62, HT-29, PC3 and MCF-7	Simionatto, et al., 2010
Peristrophe bicalyculata (Retz) Nees (Acanthaceae)	MCF-7 and MDA-MB-468 (human breast cancer) cells	Ogunwande, et al., 2010
Flower and Fruit EO of Datura metel L. (Solanaceae)	Hs 578T (human breast ductal carcinoma)	Essien, et al., 2010
Salvia pisidica Boiss. et Heldr. (Lamiacae)	HEP-G2	Ozkan, et al., 2010
Cinnamomum zeylanicum Blume (Lauraceae)	F2408 (normal rat embryonic fibroblasts) and 5RP7 (c-H-ras transformed rat embryonic fibroblasts)	Unlu, et al., 2010

Annona sengalensis Pers. leaves (Annonaceae)	A549, HT29, MCF-7, RPMI and U251	Ahmed, et al., 2010
Croton matourensis Aubl. and *Croton micans* Müll. Arg.	LoVo (colon carcinoma), Hela and X-17 (colon carcinoma)	(Campagnone, et al., 2010
Heracleum transcaucasicum (Manden.) (Umbelliferae)	Hela, LS180	(Firuzi, et al., 2010
Glycyrrhiza glabra L. (Fabaceae) and M. chamomilla	MCF-7	Ali, 2013
Trachonanthus comphoratus L. (Asteraceae)	HT29 tumour	(Awadh, et al., 2013
Caesalpinia peltophoroides Benth. (Caesalpinaceae)	U87, HCT, and A2058	(de Carvalho, et al., 2013a
Pylorae herba	SW1353	Cai, et al., (2013)
Oxandra sessilifolia R. E. Fries (Annonaceae)	HL-60 (human leukaemia cells) B16F10-Nex-2, MCF-7 and Hela	de Carvalho, et al., 2013b)
Senecio graciliflorus DC EO (Asteraceae)	A-549, THP-1, PC-3 and HCT-116	Lone, et al., 2014
Zanthoxylum bungeanum L. (Rutaceae)	Hela	Li, et al., (2013)
Artabotrys hexapetalus (L.) Bhandari (Annonaceae)	Liver carcinoma cell lines (BEL-7402)	Wang, et al., (2013a
Cecris chinesis Bunee	K-562 (human leukaemia)	Wang, et al., (2013b
Wild pepper (Piper carpense L. Piperaceae)	MDA-MB 231, A375 and HCT116	Woguem, et al., 2013
Oxytropis falcata Bunge (Fabaceae)	SMMC-7721	Yang, et al., (2013
Stachys rupestris Montbret et Aucher ex BenthSalvia heldreichiana Boiss.ex Benth (Lamiaceae)	PC-3 and MCF-7	(Erdogan, et al., 2013

Curcuma zedoaria Roscoe (Zingiberaceae)	H1299, A549 and H23,	Chen, et al., 2013b
Atractylode lancea Thunb.	MKN-45 cancer cells.	Chen, et al., 2013c
Artemisia anomala S. Moore	A549, BRO (human melanoma), MCF-7 and PC-3	Zhao, et al., 2013
Fissistigma cavaleriei (Lev.) Rehd (Annonaceae)	K562, S-180 and A549	Zhang, et al., 2012

7 Penetration enhancing activity

The volatile oils of *Rhizoma Zingiberis* (Zingiberaceae), *Flos Caryophyllata* (Myrtaceae) and *Fructus Litseae* (Piperaceae) were tested for their penetration enhancing effects. 3 %, 5 %, 7 % and 10 % of the EOs and mixtures in ratio of 1:1 were tested in an in vitro transdermal mouse skin patch model. The best penetration enhancing effects were observed with 10 % *Rhizoma zingiberis* EO, 5 % *Fructus Litsea* EO and 5 % *Flos Caryophyllata* EO. These oils were able to enhance the penetration volume from patch to mouse skin significantly (Li, et al., 2013b). The volatile oils of *Rhizoma Zingiberis*, *Flos Magnoliae* and *Fructus Litseae* were found to have good penetration enhancing activities of rotundine permeation. 2.5 % *Fructus Litseae* EO plus 2.5 % azone showed the pest effects on the penetration of rotundine using the Franz cell diffusion assay (Cui, et al., 2011).

(Yuan, et al., 2014) found, that the EO of *Asarum mialaicum* Hook.f. *&* Thomson *ex* Klotzsch (Aristolochiaceae) has penetration enhancing activities. Patches impregnated with15-35 % EO increased penetration by 10 to 20 %.

The EO of *Zanthoxylum bungeanum* Maxim. (Rutaceae) was evaluated for its penetration enhancer effects in rat skin. The EO was able to increase effectively the percutaneous absorption of the applied drugs in a dose-dependent manner (Lan, et al., 2014). The EO of *Cyprus rotundus* L. (Cyperaceae) exhibited potent penetration enhancing activities for nitracepam in a rat skin model. After treatment with more than 1 % EO the percutaneous permeability of nitrazepam was significantly increased (Zhou, et al., 2012). The EO of *Caulis sinomenii* showed significant increase of percutaneous penetration of sinomenine and triptolide (Deng, et al., 2011). Eucalyptus EO (*Eucalyptus globulus* Labill. (Myrtaceae)) showed penetration enhcancing activities on chlorhexidine (Karpanen, et al., 2010).

The volatile oils of *Flos Caryophylli*, *Semen Myristicae* and *Fructus Anisi Stellati* were found to exhibit penetration enhancing activities on ligustrazine phoshate. 3 %, 5 % and 7 % of each EO were compared to 3 % of azone, a prominent permeation enhancer. The EO of *Flos Caryophylli* showed the highest enhancing effect (Luo, et al., 2013).

The percutaneous penetration enhancement of the EO of *Eugenia caryophyllata* Thunb (Myrtaceae) was investigated on ligustrazine phosphate patch. The cumulative permeation volumes (Q_{12}) were 3.0, 4.1, 1.8 and 1.2 mg/cm^2 for concentrations of 3 %, 5 %, 7 % and 10 % respectively. Due to these results the EO of *E. caryophyllata* showed potent permeation enhancer activities (Luo, et al., 2012).

Wang, et al., (2012c) found that the EO of *Angelica sinensis* (Oliv.) Diels (Apiaceae) is able to increase the percutaneous penetration of resveratrol. At concentrations of 1.0 % and 2 % the cumulative permeation was 48.11 ± 15.93 and 16.74 ± 1.30 µg/m^2/h. The EO of *A. sinensis* was also found to raise the percutaneous permeation of nimodipine in transdermal preperations (Wang Q. , et al., 2010).

The permeation contingents were evaluated by Han, et al., (2011) using ligustrazine phosphate transdermal patches. The cumulative permeation significantly increased after treatment with the EO. At concentrations of 3 %, 5 % and 7 % of the EO the cumulative penetration quantities were 720.11, 470.13 and 115.41 µg/cm^2/h, respectively. Thus, the concentration of 5 % EO had the highest penetration enhancing effects.

Black cumin seed oil (*Nigela sativa* L., Ranunculaceae) was tested for its penetration enhancer activity on cavedilol using excised albino Wistar rat abdominal skin. At a concentration of 5 % the EO showed the most potent enhancing effects. The transdermal flux and the permeability coefficient were higher than in the control group (Saima, et al., 2010).

Volatile oils of *Alpinia katsumadai* Hayata (Zingiberaceae), *Amomum tsao-ko* and *Amomum kravanh* Pierre (both Cornaceae) were tested for

their penetration enhancing effects on strychnine through mouse skin. At a concentration of 7 % the EO of *A. katsumadai* and 5 % of *A. tsao-ko* EO were able to increase the percutaneous permeation of strychnine in the in vitro study (Shen, et al., 2010).

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