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„Essential Oils Properties, Compositions and Health Effects“

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Abstract

This review deals with the multiple health benefits of essential oils. Nowadays, volatile oils are commonly used in the food industry, not only as food flavouring agents, but also because of their ability to reduce the risk of many maladies and improve health. The tenet „Let food be thy medicine and medicine be thy food“ from Hippocrates reflects the attitude of the society today. Nowadays, customers have begun to look at food not only for the basic nutrition it provides, but also for health improvement.

Zusammenfassung

Der folgende Übersichtsbericht erläutert den gesundheitsfördernden Effekt Ätherischer Öle, welche in der Lebensmittelindustrie nicht nur als Aromastoffe eingesetzt werden, sondern auch aufgrund ihres positiven Einflusses auf die Gesundheit. Heutzutage reduzieren ernährungsbewusste Konsumenten Lebensmittel nicht nur auf den Zweck der Nahrungsaufnahme, sondern haben auch ein besonderes Augenmerk auf den gesundheitsfördernden Einfluss.

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1 Introduction

The master thesis „Essential oils: Properties, Composition and Health Effects“ is concerned with the effect of essential oils as food ingredients to improve health. First of all an overview about sources and the production of essential oils should be given. Then patterns of consumption, availability, absorption and metabolism of volatile oils will be discussed and the fourth subitem puts the focus on different health effects of essential oils.

2 Body text

2.1 Sources and production

Essential oils a group of plant secondary metabolites, are obtained only by steam distillation (according to ISO rule 9235). Those volatile compounds vary in odor and flavour. The manna of this distillation method is important because it determines the quality of the essential oil. Inappropriate production can result in the loss of bioactivity. Essential oils are concentrated liquids of complex mixtures and contain a lot of bioactive compounds. [1, 2]

2.2 Patterns of consumption

Essential oils are lipophilic compounds, which are able to cross membranes very easily. Hence, essential oils are well absorbed from the intestine, but also through the skin and the lung. Because of their transdermal and pulmonary absorption they are used for many medical applications in ointments, balms and bath additives.

2.3 Availability, absorption and metabolism

A high amount of essential oils are rapidly absorbed after dermal, oral or pulmonary administration and cross the blood-brain barrier. They are able to interact with receptors in the central nervous system (CNS) and to affect biological functions such as relaxation, sleep, digestion and so on. Essential oil constituents can be metabolized by the liver in the form of polar compounds following limited phase I enzyme metabolism by conjunction with glucuronate or sulfate. Furthermore, they can be exhaled via the lungs as volatiles or as CO_2. Sulfate as well as glucuronide forms have been detected in urine and in plasma. Because of the fast metabolism and short half-life of active compounds a minimum risk of accumulation in the body is suggested. The respiratory tract exerts the most rapid way of entry, followed by the dermal pathway. Essential oils as well as their metabolites can also be absorbed and delivered to the body through oral ingestion. [3]

2.4 Health effects

Essential oils and especially their constituents have a lot of health effects such as antibacterial, antiviral and antifungal activities. Further fields of applications are anti-cancer therapy, cardiovascular and nervous system disorders. Additionally they are used to reduce the level of cholesterol and regulate the glucose level. Besides they are useful in the treatment of gynaecological diseases. Essential oils are commonly used in the food as well as in the cosmetic industry. [4]

2.4.1 Antioxidative properties of essential oils

Nutritional properties of foodstuffs are affected by oxidation of oils. Today the tendency goes towards using natural compounds such as essential oils for producing functional food. A present study has tested *Cinnamon zeylanicum* (Lauraceae) and *Zataria multiflora* Boiss. (Lamiaceae) as two natural preservatives. The use of these essential oils prevent oxidation rate and reduce preliminary and secondary oxidation products compared with butylated hydroxyanisole (BHA). Foods which are containing fat and oils can oxidize slowly during storage. As a result, different oxidation products occur, which cause rancidity and reduction of the sensory properties of foodstuffs. Lipid oxidation and fungal growth reduce the shelf life of food products. To solve these problems manufacturers use antioxidants and preservatives. In the majority of cases the producers of foodstuff use synthetic additives such as BHA and butylated hydroxy toluene (BHT) as antioxidants, but the even low toxicity of those products have restricted their use. Recently, aromatic plants and spices serve as a source of biologically active substances such as antioxidants in foodstuffs. Today the focus is on natural antioxidants which can replace synthetic additives that might be carcinogenic. Cinnamon which belongs to the Lauraceae family provides a variety of oils with different aroma characteristics. This aromatic plant contains the highest phenolic contents and strongest antioxidant activity. The main components of cinnamon are cinnamaldehyde and methyl eugenol although the composition of essential oils is dependent on geographically conditions, the age of the plant and the drying. Studies have been shown good antioxidative and antifungal activities of *C. zeylanicum* compared with control samples. The components which are responsible for antiradical activity of cinnamon are eugenol, cinnamaldehyde, cinnamic acid and 1,8-cineole. The antifungal nature of cinnamon belongs to the high phenolic contents especially carvacrol, thymol, cinnamaldehyde and eugenol. Food manufacturers need antioxidants which resist at high temperature during baking. There is a need to find replacements of synthetic additives because synthetic compounds have a negative effect on health. Studies have been shown, that concentrations of 500 ppm of *C. zeylanicum* essential oil can be used instead of BHA. Foodstuff which contains this oil might have nutritive and functional advantages compared to BHA. Consumption of food, which includes natural additives can help us to prevent health disorders caused by oxidation, for example aging, atherosclerosis and cancerogenesis. [5]

Moreover, essential oils can also be used due to their antioxidant activities to fasten the viscosity values of edible oils. Off-flavours and the formation of toxic compounds often are related to lipid oxidation which leads to rancidity and can cause of several diseases. Lipid oxidation determines the shelf life of food. The uptake of oxygen leads to the production of reactive oxygen species which can react with lipid molecules. This reaction generates peroxyl radicals and it leads to the interaction with nucleic acids and proteins which exerts certain alterations and hence functional modifications. Antioxidants are able to delay or inhibit the oxidation of lipids through the inhibition of oxidizing chain reactions. Nowadays, antioxidants such as BHA and BHT, propyl gallate and tert. butylhydroquinone are used. Because of toxic side effects of synthetic antioxidants there is an increasing interest to find natural compounds, which can be used to prevent free radical damage. There is a growing use of essential oils as functional ingredients in food, drinks and cosmetics, because synthetic additives are potentially harmful whereas essential oils have a relatively safe status and they are widely accepted by consumers. A study has demonstrated that the essential oils from mint, laurel leaf and myrtle leaf showed antioxidant effects on edible oils. Peppermint oil mainly consists of menthol, menthone, menthofuran and menthyl acetate. The lipid peroxidation, acidity and viscosity changes of pomegranate kernel, poppy, grape and linseed were tested after the addition of essential oils from some plants. The change of peroxide, free acidity and viscosity values of those edible oils without the addition of essential oils varies from the different oils. In general, there are significant differences between all edible oils, control samples and oils with addition of essential oils as well as the levels of addition. The three tested essential oils showed nearly the same effect on peroxide and viscosity values of pomegranate kernel oil on second, fourth and sixth week. At the end of the period the free acidity value was fastened by the use of 0.05 % of myrtle leaf essential oil. The peroxide and viscosity values of poppy oil on the sixth week were lower for samples with mint and myrtle essential oils than those with laurel leaf volatile oil. But laurel essential oil is more effective on free acidity value than others. The study showed that all essential oils were effective to decrease the peroxide values of linseed oil. The use of mint and myrtle essential oils decreases the free acidity values on the sixth week, although the viscosity values differed not significantly after the addition of essential oils. For grape seed oil all of the essential oils were effective on the peroxide and free acidity values. Volatile oils can act as antioxidants by donating hydrogen to highly reactive radicals. Hence, they prevent further radical formation. [6]

Essential oils from oregano can also be used to prolong the shelf life of edible oils such as olive oil by retarding the lipid oxidation process. The aromatic plant *Origanum vulgare* L. spp *vulgare* (Lamiaceae) is used as seasoning and flavouring of fresh and preserve foods and sauces. Origanum is also famous for its therapeutic benefits such as diaphoretic, antiseptic, anti-spasmodic and it is also used in alternative and homeopathic medicine. At the beginning, essential oils were only used for flavouring and aromatizing food. Then they were also used as natural agents for food preservation and because of their effectiveness against microorganisms. It has been demonstrated that the antioxidant effect of essential oils is linked with hydroxy groups in phenolic compounds. The essential oil of oregano is rich in thymol and carvacrol, which showed a considerable antioxidant effect on the process of lard oxidation. Extra virgin olive oil is very popular by customers because of its sensory properties and nutritional benefits. These properties are primarily related to the fatty acid composition as well as to the high content of oleic acid and to the balanced ratio of saturated and polyunsaturated fatty acids. Hence, olive oil is proposed as a functional food which can help to prevent several diseases such as cancer and atherosclerosis. For this reason, there is an increasing interest in the prevention of the quality of this oil during its shelf life. The major compounds of oregano essential oil are trans-sabinene hydrate, thymol and γ-terpinene. The results of the study showed that the essential oil from oregano exerts a protective effect of lipid oxidation of olive oil. The formation of free fatty acids (FFAs), mono- and di-glycerides, and glycerol results from the hydrolysis process in fats and oils. [7]

Essential oils are also able to protect beef patties against lipid oxidation. Beef patties are consumed in large amounts as fast meals. Because of the increasing prize of raw meat material, low-cost materials such as mechanically deboned poultry meat (MDPM) was used instead. Although this low cost material is known for its excellent nutritional and functional properties which are suitable for formulation of several meat products, there is a rapid onset of oxidative rancidity which leads to off-flavours and off-odors. Products which are manufactured with MDPM can be stored for only shorter periods, because of the rapid onset of oxidation and high microbial load. Natural antioxidants have been introduced to improve lipid stability as well as sensory properties of food. Studies have been shown that beef patties which were prepared with MDPM exhibit on the one hand a significant reduction in protein content and on the other hand an increased fat content. Lipid oxidation in meat products can be indicated with the presence of thiobarbituric acid reactive substance. Those beef patties which were manufactured without MDPM showed a lower value of this substance. The higher concentration of this substance can be linked with the higher fat content which can speed up lipid oxidation. The preparation process of MDPM leads to the extraction of high amounts of lipids from bone marrow. Additionally, the reduction of size of MDPM particles during extrusion leads to the addition of oxygen. Therefore, lipid oxidation of polyunsaturated fatty acids which are mainly present in phospholipids derived from bone marrow was promoted. The content of polyunsaturated fatty acids and hemoproteins is significantly higher in mechanically deboned meat than in hand deboned meat. Hemoglobin possesses potent pro-oxidant effects. During mechanical grinding haem or iron can be released from proteins which can speed up peroxidation of polyunsaturated fatty acids. It has been proved that the addition of essential oils from marjoram and rosemary are able to decrease the concentration of thiobarbituric acid reactive substance of beef patties. By the use of essential oils from rosemary the rancidity of heat-treated turkey meat was inhibited. Moreover, the oxidation process during cooking is inhibited when rosemary extract is added to MDPM. Essential oils from rosemary and marjoram are more effective than BHT, this fact depicts the superiority of herbal essential oils to synthetic antioxidants. Additionally, beef patties with antioxidants exhibit a significantly better flavour. Without addition of antioxidants rancid flavour in beef patties was detected. Secondary products of fatty acid auto-oxidation such as aldehydes, ketones, hydrocarbons, esters, lactams and so on are generated too, because of the high potential of fatty acids to get oxidated. The reduction of lipid oxidation decrease the rate of flavour deterioration. In conclusion, the addition of essential oils significantly increased the acceptability of beef patties after preparation as well as during frozen storage. [8]

Besides, essential oils from *Nigella sativa* L., known as black seed or black cumin, is also able to reduce lipid oxidation. This dicotyledon plant belongs to the family of Ranunculaceae and is famous for its use as spice and food preservative. Seeds of *N. sativa* have been used to treat and prevent several diseases and as well as a supplement to promote good health. Black cumin is an annual flowering plant growing in southwest Asia. Its large fruits contain many seeds. Essential oil from black cumin mainly consists of thymoquinone, p-cymene, carvacrol, t-anethole and 4-terpineol. On the one hand oxidation is necessary for nearly all cells in the body to provide energy, but on the other hand, uncontrolled oxidation leads to the production of free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (NOS). Those free radicals can override the antioxidant capability of the target cells which results in oxidative stress. Therefore, the damage of macromolecules such as DNA, the production of mutated tumor-suppressor genes as well as the induction of cell death is the result. Free radicals are linked with several diseases such as cancer, ischemia, diabetes, atherosclerosis and so on. These pathological events are related with cardiovascular, neurodegenerative as well as carcinogenic processes. Degenerative disorders can result from lipid peroxidation which is an autocatalytic mechanism leading to the oxidative destruction of cellular membranes. There is evidence that the oil of *N. sativa* is able to inhibit lipid peroxidation of biological membranes. This seed oil is known to improve the antioxidant defense system and to prevent the lipid peroxidation induced liver damage. Its active ingredient thymoquinone is able to inhibit lipid peroxidation. Moreover, lipid peroxidation as well as H_2O_2 are responsible for degradation, loss of deformability and an increased osmotic fragility in erythrocytes. Because of their antioxidant potential they are able to suppress nitric oxide production and act as a superoxide anion scavenger. The use of *N. sativa* oil decreases the risk factors of several diseases, it tends to normalize the concentration of lipid peroxide (LPX), lactate dehydrogenase (LDH), glutathione (GSH) and superoxide dismutase (SOD). The positive effect of the oil is also reflected by enhanced activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and a decreased level of lipid peroxides. The overall antioxidant protection capacity of the body is improved by supplementation of *N. sativa*, it exerts a protective effect against nephrotoxicity and hepatotoxicity. [1]

2.4.2 Inhibition of foodborne pathogens by essential oils

Foodborne illness which is caused by microorganisms is a growing public health concern. The percentage of people which are suffering from food borne illness is up to 30 %. Unsafe food is responsible for illness and results in several deaths every year. Nowadays, there is an increased concern of food safety and a demand from customers of natural products which are free from synthetic additives. Today, the use of natural antimicrobial compounds, such as essential oils, herbs and spices for food preservation, play a big role. Essential oils offer a relatively safe status and a potential for multi-purpose functional use. [9] Especially essential oils from the Lamiaceae and Apiaceae families exert bactericidal properties against microorganisms contaminating food products, therefore they are considered as natural food preservatives. The biological activity of essential oils is closely linked to their chemical compounds. Additionally, the widest spectrum of action as well as the greatest antibacterial activity is shown by phenolic compounds, e.g. thymol and carvacrol, which occur in plants from the Lamiaceae family. Above all *Thymus vulgaris* L., *Origanum vulgare* L. and *Satureja hortensis* L. play an important role. The phenylpropanoid eugenol, a phenolic compound, is also known for its antimicrobial properties. Eugenol occurs in essential oils of clove, cinnamon leaves and so on. Essential oil compounds, such as carvacrol, thymol, eugenol, cinnamaldehyde, and cinnamic acid, are used in food to control natural spoilage process as well as to prevent growth of microorganisms. Microorganisms can produce substances which are harmful to humans, such as toxic and carcinogenetic metabolites. [4]

Essential oils are important to avoid the occurrence of *Listeria monocytogenes* in ready-to-eat poultry products. *L. monocytogenes* can occur in a variety of foods. The problem is that most of the ready-to-eat foods receive little or no final heat treatment before eating, because a high amount of them are labeled as fully cooked. It has been reported that illness can occur if ready-to-eat products are not reheated before consumption. Furthermore, contamination of ready-to-eat products with *L. monocytogenes* has resulted in a number of recalls. The contamination of these products is a great challenge for the food industry. When ready-to-eat meats are contaminated with *Listeria* these bacteria can survive at refrigeration temperature and grow during temperature abuses, e.g. during transportation or consumer storage at home. The addition of herbal extracts may control the survival and growth of *Listeria* in ready-to-eat products. Herbs are usually used as food ingredients and they are known for their broad-spectrum activity on Gram-positive and Gram-negative bacteria. It has been proven that eugenol is able to inhibit *L. monocytogenes*, *Campylobacter jejuni*, *Salmonella Enteritidis*, *Escherichia coli* and *Staphylococcus aureus*. But the tests have been conducted on various agar media, so the effect on food products can be different. Hence, the antimicrobial activity of clove oil against *L. monocytogenes* was tested on cooked chicken. The treatment with clove oil showed a significant reduction in final *L. monocytogenes* populations at 5 °C and 15 °C storage compared to the control. In general, the growth rates were significantly reduced by clove oil treatment for most of the *Listeria* strains. The application of 1 % clove oil on the surface of Frankfurters coupled with low temperature storage is able to reduce the contamination with *L. monocytogenes*. [10]

Essential oils constituent such as (E)-methylisoeugenol und elemicin could be used as food additives because of their activity against *C. jejuni. Campylobacter* is responsible for bacterial gastro-enteritis in humans and it is recognized as the most identifiable infection preceding Guillan-Barré syndrome. This disease can result in immune-mediated disorder and acute flaccid paralysis. Several animals are colonized by this zoonotic pathogen. Human can be infected by the consumption of poultry, raw milk, water or by means of the direct zoonotic transmission from contact with infected pets. To decrease or even eliminate the population of *Campylobacter* on raw poultry meat, several treatments such as washer systems with chlorinated water, chemicals (Na_3PO_4) or irradiation were used. Nowadays, there is a need to find new natural antibacterial substances instead of antibiotics which were used in animal feeding as a growth promoter or preventive agent. There is an increasing interest to look for alternatives to deal with food-borne pathogens. Essential oils from *Daucus carota* L. which belongs to the family of Apiaceae showed antibacterial properties. Recent studies have shown that essential oils from wild *D. carota* from Corsica possess the ability to inhibit the growth of *C. jejuni*. The oil mainly consists of (E)-methylisoeugenol, β-bisabolene, elemicin and α-pinene. In most cases patients recover from infections with *C. jejuni* without antibiotic treatment, but patients which suffer from persistent enteritis must be treated with antibiotics such as erythromycin or fluoroquinolones. Because of the increasing number of antibiotic resistance in *C. jejuni* there is a growing interest to find new substances which are effective against this germ. In conclusion, (E)-methylisoeugenol and elemicin could be used as food additives to decrease *Campylobacter* in poultry. [11]

Moreover, essential oils could be used for the reduction of biogenic amines as well as a flavouring agent in Gouda cheese, which has a positive health effect. Different concentrations of the essential oil from *Zataria multiflora* Boiss. (Lamiaceae) were added to milk, to test the effect of this oil on biogenic amines production such as tyramine and histamine and microbial counts in Gouda cheese. Thus, the concentration of tyramine and histamine was significantly reduced at the end of maturation period compared to the control group. The higher the concentration of the essential oil the higher was the decrease in biogenic amines and microbial counts. *Z. multiflora* essential oil was most effective against yeasts, but there was only a low reduction in Enterobacteriaceae counts. Biogenic amines are organic bases with low molecular weight which can be formed during the metabolism in animals, plants and microorganisms. The decarboxylation of certain free amino acids leads to the formation of biogenic amines. Biogenic amines affect physiological functions such as immune response, brain activity and gastric acid secretion. If biogenic amines occur in big amounts in food, they can cause health damage. Undue oral intake of biogenic amines can result in headaches, nausea as well as alterations of the blood pressure. Biogenic amines can be converted into nitrosamines in the presence of nitrites. Those nitrosamines depict potential carcinogens. The toxicity of biogenic amines can be increased by food which is rich in biogenic amines, by alcoholic beverages or by the inhibitory effects of mono amine oxidase inhibitors. Furthermore, there are also interactions among biogenic amines. It is extremely difficult to determine biogenic amines and in most food stuffs there are no legal limits concerning biogenic amines concentration. The synthesis and accumulation of biogenic amines in foods should be controlled, because of their toxicological effects. Cheese is often associated with histamine poisoning. Several cheeses show an appropriate kind of foodstuff for the accumulation of biogenic amines because of a longer ripening period. The longer the ripening time the higher is the concentration of biogenic amines. The content of biogenic amines in cheese is determined by several factors such as milk pasteurization, hygienic conditions, ripening and storage temperatures, time of ripening and so on. The production of biogenic amines in cheese is mainly dependent on the presence of microorganisms with decarboxylase activity. Moreover, Gram-negative bacteria which can occur in milk are able to form histamine, putrescine and cadaverine. There are various methods to reduce biogenic amines in food, such as food additives, high hydrostatic pressure, irradiation and so on. Essential oils are natural food additives with antibacterial and health-improvement properties. Biochemical and microbiological changes during the ripening period of Gouda cheese result in the production of biogenic amines. The main component of the essential oil is carvacrol, followed by γ-terpinene, α-pinene and eucalyptol. Studies showed that increasing concentration of essential oil lowers the concentration of biogenic amines such as tyramine and histamine in Gouda cheese. Concentration of 0.1, 0.2 and 0.4 % of essential oil leads to a significant reduction of biogenic amines. Histamine formation depicts the most common food borne intoxications associated with biogenic amines. Although the histamine content in the control group is lower than the toxicological limit, it can depict a health problem for patients which are consuming mono amino oxidase inhibitors, for allergic persons and persons which eat a lot of cheese. Enterococci often occur in cheese, because some of them are resistant to milk pasteurization. There is a correlation between the presence of enterococci and biogenic amines. In the first days of ripening mesophilic lactobacilli represent the dominant bacteria. Counts of mesophilic lactobacilli decreased significantly by the use of essential oils. Although enterobacteriaceae are destroyed by the use of pasteurization, inferior hygienic milk-handling as well as manufacturing practices can result in contamination of cheese. Enterococci and enterobacteriaceae are known as the main producers of biogenic amines in cheese. Hence, the occurrence of biogenic amines could be used as an indicator of bad manufacturing. Furthermore, the study showed that yeasts were most susceptible to the essential oil of *Z. multiflora*. Several yeast species seemed to be able to build up tyramine and histamine. In conclusion, the use of *Z. multiflora* essential oil results in reduced biogenic amines content and microbial counts in cheese. [12]

2.4.3 Essential oils and spasmolytic activities

Present studies have shown promising spasmolytic activities from *Cuminum cyminum* L. (Apiaceae). Cumin is a herbaceous plant, which is cultivated almost throughout India. The essential oil is extracted from ripe fruits through hydrodistillation. Generally, cumin is used as antioxidant and flavour. Besides these properties it also acts antiseptic, analgesic, anti-inflammatory and sedative and is used against stomach disorders, diarrhea and spasms. The anti-spasmodic activity was tested on isolated guinea pig ileum. Hydrodistilled fruit extract of *C. cyminum* was used in the study. At the beginning concentration dependent responses of acetylcholine on pig ileum were recorded. Acetylcholine induces dose dependent spasms. The treatment of hydrodistilled fruit extraction of *C. cyminum* showed distinctive anti-spasmodic activity. The anti-cholinergic drug atropine was used as standard anti-spasmodic agent. The standard agent as well as the hydrodistilled extract of *C. cyminum* showed the same anti-spasmodic action. These results showed that acetylcholine alone causes contraction of the ileum but when acetylcholine was given in combination with hydrodistilled fruit extract there was a significant decrease of contraction noted. *C. cyminum* causes a high degree of spasmolytic activity by blocking cholinergic receptors, so this fruit extract exhibits promising anti-spasmodic activity. [13]

2.4.4 Essential oils and antifungal activities

Essential oils from cinnamon are used in active paper packaging against food spoilage caused by *Rhizopus stolonifer*. The prevalent spoiler of white bread and bakery products are *Rhizopus stolonifer*, *Aspergillus* and *Penicillium* genera, due to the production of mycotoxins, off-flavour formation and revolting appearance as results of those fungi. Spores of *Rhizopus stolonifer* are ubiquitous in the air and grows on bread and fruit, especially when bread is stored in an enclosed and humid environment. Besides the use of essential oils as food preservatives to extend the shelf life, active packaging becomes a famous alternative to control unwanted molds in food. There is a growing interest of using active paper packaging with essential oils as antimicrobials. For this packaging an active wax or solid paraffin coating containing essential oils from clove, cinnamon and oregano were used. Those compounds are able to pass on the antimicrobial activity to its packaging material. It has been proven, that the active components of the cinnamon essential oil are partially transferred to bread slices and that cinnamaldehyde exerts the strongest antimicrobial activity. Active paper packaging is a good alternative for protecting bread from fungal infestation which is inhibited during the lag-phase. The impact of active paper is closely linked with the final concentration of cinnamaldehyde which is found in bread and it seems that migration via headspace is much more significant, compared with direct migration through direct packaging-food contact. [14]

The essential oil from dill (*Anethum graveolens* L.) (Apiaceae) is also famous for its antifungal activity. This volatile oil is helpful in the prevention of fungal spoilage of cherry tomatoes, for which especially *Aspergillus* and *Alternaria* are responsible. If fresh fruit and vegetables are stored in a high moisture and high temperature environment, they are highly susceptible to be attacked by pathogenic fungi which are not the only ones responsible for food decay. In the worst case, several of these microorganisms represent serious risks for consumers, because they produce dangerous mycotoxins. The use of synthetic preservatives to control fungal spoilage of food has caused serious environmental and health problems, such as carcinogenicity, teratogenicity and high and acute toxicity. Hence, there is an urgent need to look for safer alternative protectants instead of synthetic pesticides and essential oils are recognized as safer antifungal agents. The advantage of essential oils is that they are from natural origin and that they have a low risk to develop resistance to pathogenic microorganisms. *A. graveolens*, a plant which belongs to the Umbelliferae family is known as a flavour in food and beverages, because of its spicy aroma. This spice is famous for several pharmacological properties, such as antibacterial, anti-hyperlipidemic and anti-hypercholesterolemic effects. Studies have demonstrated that mycelia growth and fungal development in cherry tomatoes was reduced with increasing concentrations of essential oils from *A. graveolens.* The percentage of infected fruits is significantly reduced by the use of this essential oil. The antifungal activity may be linked with the hydroxyl groups in antimicrobial components which can form hydrogen bonds with active enzymes, thus resulting in deactivation. The essential oil from *A. graveolens* is a potential fumigant during storage and extended transport period. [15]

2.4.5 Essential oils and acaricidal activity

Furthermore, essentials oils are also famous for their acaricidal activity. They are useful as preventive agents to control the growth of stored-food mites populations. Food mites, such as *Acarus siro* and *Tyrophagus putrescentiae* are found in food grains as well as in stored foods with a high fat and protein content. Those food mites lead to significantly economic losses and to a reduction of nutrient content. There are physical and chemical methods to exterminate house dust and stored food mites. A key factor to control mites is to reduce the relative humidity as well as applications of chemicals such benzyl benzoate, N,N-diethyl-m-toluamide (DEET) and Dibutyl phthalate. Those methods are effective but the repeated use of them leads to several problems such as potential mite resistance and unwanted activity against non-target organisms. Hence, there exists growing interest in the search for new methods to control house dust and stored food mites. Plant essential oils are known for their biological activity against mites without adverse effects. Therefore, essential oils display a potential source of alternative mite-controlling agents. The plant, *Dioscorea japonica* Thunb. (Dioscoreaceae) which has been used as an edible food and traditional medicine, possesses a lot of biological activities such as antifungal, anti-hypertensive, anti-mutagenic, antioxidant, immunmodulatory and acaricidal ones. The active component of the essential oil from *D. japonica* namely 2-hydroxy-4-methoxyacetophenone is more toxic than DEET against mites and possesses other pharmacological effects such as anti-aggregatory, anti-inflammatory, antioxidative and anxiolytic properties too. Studies have shown that 2-hydroxy-4-methoxyacetophenone is more effective than synthetic acaricides against *D. farinae*, *D. pteronyssinus*, and *T. putrescentiae* and has the potential to be used as a fumigant against house dust and stored food mites, which would mitigate the allergic symptoms experienced by humans. [16]

2.4.6 Essential oils and insecticidal activities

Furthermore, essential oils can also be used as alternatives for currently used chemical insecticides. Stored pulses are often infested with pests such as *Callosobruchus maculatus*, which is responsible for damage of legumes. To control pest infestation in grain and other dried foodstuff, fumigation and application of chemical grain protectants are commonly used and again these synthetic insecticides for controlling stored products has to be called in question, because of their adverse effect on environment, human health, food contamination and insecticide resistance. Hence, essential oils which have multiple functions can act as antimicrobial, antifungal, antitumor, insecticidal agents and so on. Kaolin which is a natural mineral, is effective on stored products pests, and essential oils from *Mentha pulegium* L. (Lamiaceae) and *Zingiber officinale* Roscoe (Zingiberaceae) have shown acute toxicity against different stages of *C. maculatus*. The insecticidal activity of essential oils from *M. pulegium* against *C. maculatus* was stronger than the insecticidal activity of *Z. officinale*. In most cases monoterpenoids are the insecticidal constituents of essential oils, because of their low toxicity, high fumigant activity, fast degradability properties as well as their regional availability. Studies have shown that those essential oils exhibit their fumigant toxicity on egg, larvae and adult of *C. maculatus*, due to inhibition of different biosynthetic processes on the insect´s metabolism. Essential oils such as linalool, terpineol, carvacrol and myrcene exert insecticidal effects on some stored products pests too. The higher the concentration of essential oils, the higher the mortality of *C. maculatus*. The combination of essential oils with kaolin showed a synergistic effect and it exhibits high acute toxicity against different stages of *C. maculatum*. [17]

Besides, *Citronella* is also known as an effective insect repellent, which is used in food packaging. Carrying insects by packaging exhibits also a problem and leads to spoilage and loss. Methyl bromide is used as a fumigant to control insect infestation, but contributes to the depletion of the earth´s ozone layer. Another negative side effect of using those insecticidal fumigants is that dead insect carcasses remain in the packaging. Hence, the use of insect repellents in packaging reduce the presence of insects and the necessity for chemical fumigants. Some studies deal with the controlled release of insect repellent and the incorporation of insecticides into packaging materials. There are two opportunities of the incorporation of insect repellents into paper based packaging, either to incorporate methyl salicylate into a coating for paperboard or to treat the surface of papers and adhesive tapes, with a combination of plant substances which act as insect repellents. Insect repellents could be applied on carton boards for example for breakfast cereals, confectionary and so on. Studies have shown that cartons which were treated with citronella exhibit lower infestation levels of beetles than the control cartons. Citronella which is already used for food flavouring also possesses the potential to be used in food packaging. [18]

2.4.7 Essential oils avoid postharvest decay

Essential oil constituents, such as eugenol, menthol or thymol, can be used in combination with modified atmosphere packaging (MAP) to improve the safety and quality of table grapes. Table grapes, also called *Vitis vinifera* L. (Vitaceae) which belong to the group of non-climacteric fruit, show several problems during postharvest storage, e.g. loss of quality, weight loss, color changes and accelerated softening. Furthermore, rachis browning as well as high incidence of berry decay can occur during prolonged storage. Gray mold, which is caused by *Botrytis cinerea* is the most common disease of table grapes. This uncontrolled infection is characterized by rapid spreading of aerial mycelium to adjacent berries. Hence, synthetic fungicides such as sulfur dioxide are known to kill both spores and mycelia. However, the necessary concentrations can lead to injuries of rachis and berries and browning. Moreover, the residue of sulfite is also a problem. Therefore, the food and drug administration (FDA) has limited the use of fumigation with SO_2, while the European Union has even forbidden the application of it. And again human health concerns and environmental pollution supports the search for new strategies as alternatives to control postharvest decay. High CO_2-concentration under controlled atmosphere for instance was used to reduce decay, but this method has side effects, such as rachis-browning and off-flavours. Also, modified atmosphere packaging alone or in combination with acetic acid, chlorine gas or SO_2 was used to reduce decay. Besides the use of essential oils from *Thymus*, *Syzygium* and *Mentha* as natural preservatives in cheese, bakery products as well as in meat, they are also able to avoid food spoilage during storing. Studies have shown that the weight loss was reduced by the use of MAP conditions in combination with antimicrobial compounds. Among the tested essential oils, eugenol treatment led to the lowest weight loss. It has been shown that the addition of antimicrobials inside the packages delayed the loss of firmness. Especially eugenol was most effective on maintaining berry and flesh firmness. Menthol, eugenol and thymol were effective in reducing decay, whereas eugenol was even most effective in reducing mould and yeast counts. These essential oils constituents were used to improve the effectiveness of MAP on preserving table grape quality and safety and are therefore a good alternative to synthetic fungicides. Moreover, the antioxidant activity of essential oils might reduce dehydration, chlorophyll degradation as well as the occurrence of browned polymers, which are responsible for stem browning. The mechanism of action of those essential oil constituents is linked with their hydrophobicity which allows them to penetrate the lipids of the cell membrane, resulting in the disturbance of its integrity, e.g. change of their permeability for cations. The antimicrobial activity is closely linked with the presence of the phenolic ring. Based on this fact, the lower activity of menthol compared to eugenol and thymol can be explained. Moreover, the combination of MAP with essential oils has a synergistically effect on inhibiting the microbial growth in meat, bakery products and sweet cherry as well as the microbial spoilage of table grape during storage. Slight odor from those compounds can be detected immediately after opening the packages, but this smell disappears rapidly. After tasting the grapes, it has been shown that eugenol exerts the lowest residual flavour. [19]

Moreover, studies showed that the decay of strawberries can also be reduced by the use of eugenol, menthol and thymol. Besides the reduced decay on treatment with those essential oil constituents, they also lead to higher amounts of sugar, organic acids, total phenolics, anthocyanins as well as flavonoids in berry fruits. All of them show antimicrobial activities and antioxidant capacities. Studies have shown that thymol exhibits the highest antioxidative properties resulting in slow berry decay. The treatment of the fruits with these constituents also enhanced the anti-proliferative effect of the fruits on colorectal adenocarcinoma as well as they reduce the oxidative stress caused by decay organisms. [20]

Essential oils can also be used as biofungicides for the treatment of postharvest anthracnose in tropical fruits such as banana and papaya. Those climacteric fruits are perishable and susceptible to postharvest diseases such as anthracnose, which is caused by *Colletotrichum* spp.

Immature fruits are infected by the fungus, while symptoms only appear after ripening. Normally, synthetic fungicides in combination with hot water are used to decrease postharvest diseases, but the nutritional quality and sensory properties are affected by heat treatment. On the other side, the continuous use of synthetic fungicides can lead to fungicide-resistant strains of the pathogen. The residue of fungicides on the surface of fruits can cause serious threats to the consumer and to the environment. Hence, there is a need to find alternatives to control postharvest diseases. Edible coatings are able to provide selective barriers against respiration, moisture loss and decay. Those coatings provide several advantages such as edibility, bio-compatibility, being non-toxic and low cost. Gum arabic is a well known bio-degradable polymer, which can be used as film or coating component. This bio-polymer is obtained from stems of the Acacia tree and consists of galactose, rhamnose, arabinose and glucoronic acid. Nowadays, natural antimicrobial agents, such as essential oils, are incorporated onto the packaging and can be released into the packages slowly. It has been reported, that volatile oils of lemongrass and cinnamon exert antifungal properties against *C. musae* of banana. In vitro studies showed that essential oils from lemongrass and cinnamon alone exhibit the greatest effect against anthracnose, especially bananas responded well to the treatment. Moreover, the essential oil of cinnamon which contains the very potent antifungal cinnamaldehyde was more effective against anthracnose as the oil of lemongrass. The use of gum arabic as an edible coating in combination with lemongrass and cinnamon showed the greatest potential to control anthracnose. In vitro as well as in vivo studies showed that coating treatments with 10 % gum arabic combined with 0.4 % cinnamon showed the greatest effect. The growth of microorganisms is inhibited by means of the interference in biological processes involving electron transfer and reaction with nitrogen containing compounds. In conclusion, the composite treatment of 10 % gum arabic and 0.4 % cinnamon might be suitable as a very potent postharvest bio-pesticide. [21]

2.4.8 Essential oils and anticancer activities

Cancer is a worldwide disease which can occur at any age and it is the second cause of mortality particularly in low income countries. Till 2030 the cancer mortality could increase by 50 % to reach 15 million worldwide.

There is a relationship between the production of reactive oxygen species to the origin of oxidation and inflammatory. These facts can lead to cancer. Oxidative stress can act as a DNA-damaging agent which can furnish an increasing mutation rate within cells promoting oncogenetic transformation. ROS activate signalling pathways which contribute tumor development by means of regulation of cellular proliferation, angiogenesis and metastasis. [1] It is worth to note that many cytotoxic molecules of plant origin, are used in chemotherapy, e.g. thymoquinone (as an active ingredient of *N. sativa*), and possess chemo-preventive potential. It is to be considered that 30-40 % of all kinds of cancer can be prevented with a healthy lifestyle and dietary measures and it is obvious that nutrition has an impact on the cancer process. There are dietary components which are able to promote cancer progression and there are some which act as chemopreventive agents. There is a large amount of naturally occurring compounds with cancer-preventive effects. There are two mechanisms by which chemopreventive agents can exert their anticancer effects: anti-mutagenic and anti-proliferative. DNA damage is prevented by anti-mutagens because they decrease the formation of mutagens and carcinogens. Chemopreventive agents are known for their anti-proliferative effects by means of induction of cell cycle arrest or apoptosis, inhibition of angiogenesis, induction of terminal differentiation and inhibition of oncogene activity or DNA synthesis. *N. sativa* exerts a positive effect regarding mediating inflammation and cancerous cell growth. Nuclear factor kappa B activation was decreased by thymoquinone in a dose-dependent manner. Thymoquinone shows a safe alternative to treat colon cancer. The chemotherapeutic effect of this substance is comparable with the synthetic 5-fluorouracil. The inhibiting effect of the essential oil from *N. sativa* on colon carcinogenesis may be linked with the suppression of cell proliferation in the colon mucosa. The essential oil of black cumin seeds is known for their cytotoxic and apoptotic/necrotic properties in a cancer cell line. An animal study has shown that the supplementation of *N.*

sativa seeds to the diet is able to protect against oxidative stress, inflammatory response as well as carcinogenesis. Furthermore, this study reported that the daily intake of these seeds (and thus of the volatile oil) results in the reduction of chromosomal aberrations and damaged cells. Additionally, animal models showed that thymoquinone blocked angiogenesis in vitro and in vivo, thus preventing the growth of cancerous cells. In conclusion, the anticancer and anti-inflammatory properties of *N. sativa* and its essential oil containing thymoquinone, may be attributed partly to the suppression of NF-kappa B activation pathway. This essential oil can also be considered as a potential immuno-suppressive agent. Because of its nutritional quality *N. sativa* is a potential source of diet-based strategies, which may play a role in improving human health. [1]

Besides, monoterpenes which are components of nearly all essential oils and especially of citrus fruits can be used to prevent cancer. Several dietary monoterpenes are known for their antitumor activity. It has been shown that (+)-limonene exerts chemopreventive activity against rodent mammary, skin, liver, lung and forestomach cancers. Hence, the chemotherapeutic properties are under evaluation in phase I clinical trials. The antitumor activities of monoterpenes may be linked with several mechanisms of action. The preventive activity of monoterpenes during the initiation phase of mammary carcinogenesis is related to the induction of phase II carcinogen-metabolizing enzymes resulting in carcinogen detoxification. (+)-Limonene results from the cyclisation of geranylpyrophosphate catalyzed by limonene synthase and is used as a precursor of other oxygenated monocyclic monoterpenes such as carveol, carvone, menthol, perillyl alcohol and perillaldehyde. (+)-Limonene, the main constituent of orange oil, for example, is widely used as a flavouring agent for fruit juices, soft drinks, ice cream and so on. The monoterpenes (+)-limonene and perillyl alcohol, its metabolism product, showed a high degree of oral bio-availability. Limonene is metabolized by phase I and phase II enzymes to oxygenated metabolites, such as perillic acid and dihydroperillic acid as well as limonene-1,2-diol.

Chemopreventive remedies can act as cancer blocking and/or suppressing agents. Blocking agents interfere during the initiation phase of carcinogenesis, with the purpose that the interaction of chemical carcinogens with DNA is prevented. These effects are likely due to the induction of phase I and phase II carcinogen-metabolizing enzymes which results in carcinogen detoxification. Whereas, suppressing chemopreventive agents are able to prevent the outgrowth of initiated cells during the promotion phase of carcinogenesis. Limonene can induce CYP 2B1 and CYP2C and epoxide hydratase. Moreover, limonene is able to induce glutathione-S-transferase and Uridin-5'-diphospho-glucuronyl transferase (UDP-glucuronyltransferase). Besides, the cancer suppressing property of monoterpenes leads to the inhibition of tumor cell proliferation and acceleration of the rate of tumor cell death, the so called apoptosis. The chemopreventive effect during the promotion phase is linked with a significantly increase in tumor cell death by apoptosis, a programmed cell death. Furthermore, the mevalonate metabolism is also affected by monoterpenes. It has been reported that monoterpenes, such as limonene and menthol, are able to inhibit hepatic 3-hydroxy-3-methylglutaryl (HMG) CoA-reductase activity and reduce serum cholesterol. In conclusion, several dietary monoterpenes exert chemopreventive effects. Monoterpenes show ideal chemopreventive properties, such as antitumor activity, commercial availability, low cost, oral bio-availability and low toxicity. Because of this reason, monoterpene studies are proceeding in human clinical trials for chemotherapeutic activity. [22]

Besides, the essential oil eugenol is another phenolic phytochemical possessing a health promoting potential. It is an active compound of the aromatic plant *Syzigium aromaticum* (L.) Merr. et L. M. Perry (Myrtaceae) and belongs to a broad class of nutraceuticals and is also used in medicine as a local antiseptic and anaesthetic. This essential oil constituent also possesses antioxidant, anti-mutagenic, anti-genotoxic, anti-inflammatory and anticancer properties. Eugenol is able to induce apoptosis in melanoma, skin tumors, osteosarcoma, leukemia, gastric and mast cells. Dietary agents can be used for chemoprevention and especially phenolic phytochemicals which are found in plants show a great health-promoting potential. Those substances belong to the broad class of nutraceuticals and eugenol, traditionally used in Asian countries for its antiseptic, analgesic and anti-bacterial properties, is such an active phenolic component. Moreover, this essential oil has been used as flavouring agent in cosmetics and food products. It has been reported, that the oral feeding of eugenol exhibits anti-genotoxic activities against chemicals such as cyclophosphamide, procarbazine and urethane. The acceptable daily intake of eugenol is 2.5 mg/kg body weight for humans. Aside from that, eugenol is proclaimed as safe and it is considered as non-carcinogenic and non-mutagenetic and on the contrary showed anticancer activity against various cancer cell lines. Thus, it is claimed as a possible candidate to prevent cancer. In addition, the molecular mechanism of eugenol-induced apoptosis in tumors is described accurately. Eugenol belonging to the allyl-benzene class of chemical compounds is well soluble in organic solvents and is the main compound of the essential oils of cloves which are native in Indonesia, Madagascar and India. [23]

Besides, the essential oil of wild celery (*Smyrnium olusatrum* L., which belongs to the family of Apiaceae) can also act as a model for the development of chemoprotective agents. Wild celery is a biennal plant, which was used for many centuries as vegetable, because of its characteristic smell and flavour, it can be added as a condiment to soups and

sauces and especially the fresh leaves were used as raw, green vegetables with a pleasant flavour similar to celery, but sharper and therefore it was most common in gardens for a long time till it was abandoned after the introduction of celery. The flower buds are still used in salads in the UK. The essential oil is obtained from the inflorescens with high levels of furano sesquiterpenoids, such as isofuranodiene and germacrone. These substances show noteworthy cytotoxic activity on the human colon cancer cell lines and are hepatoprotective as well as anti-inflammatoric. Analyses showed that wild celery oil and isofuranodiene are able to induce cell cycle arrest and apoptosis in colon cancer cells in a concentration dependent manner. In vivo studies also showed that this essential oil inhibits the growth of uterine cervical and sarcoma tumors as well as breast cancer tumors with efficacy comparable to that of cyclophosphamide. Thus, wild celery can also be used as a potential source for the development of chemopreventive agents. [24]
Essential oil constituents, such as citral, are also known for their anticancer potential. Citral consists of two isomeric acyclic monoterpene aldehydes namely geranial (trans-citral, citral A) and neral (cis-citral, citral B) the double bond in conjunction with an aldehyde group is responsible for the proapoptotic activity. Citral can be obtained from herbs such as lemongrass, melissa and verbena. This key component is commonly used as a food additive. Studies showed that concentrations of 44.5 µM citral induced apoptosis in cancer cell lines, a concentration which is comparable to the one of citral in a cup of tea prepared from 1 g of lemongrass. Apoptosis is linked with DNA fragmentation and induction of caspase-3 catalytic activity, whereby the αβ-unsaturated aldehyde group is responsible for this apoptotic effect, it might be a core structure for the design of pro-apoptotic drugs. [25]

Essential oils also have the potential to prevent foodborne infections as well as carcinogenesis both which can result from heat-processed meat products.

The occurrence of *Escherichia coli* in uncooked beef patties can result in illness of the consumers as ground beef products are common vehicles for foodborne illnesses. This problem is linked with the failure to cook meat products thoroughly. Infection with *E. coli* furnish symptoms, such as diarrhea, hemorrhagic colitis, hemolytic uremic syndrome and even death. However *E. coli* can be inactivated by cooking meat at high temperatures. Cooking of protein rich foods at high temperatures at the other hand exhibits the disadvantage of formation of heterocyclic amines which are responsible for several cancers in humans. Studies showed that there is a link between the consumption of red meat and human esophageal squamous cell carcinoma. There is also a direct connection with the intake of 2-amino-3,4,8-trimethylimidazo[4,5 f]quinoxaline and gastric cancer. The risk of advanced prostate cancer can be forced by the consumption of red meat cooked at high temperature too. Further investigations showed that the consumption of red meat and saturated fat may be linked with increased chronic liver disease and risk of hepatocellular carcinoma. All of those risks are reduced by the consumption of white meat. 2-Amino-1-methyl-6-phenylimidazo[4,5 b]pyridine showed estrogenic effects in human breast cancer cells at sub-nanogramm levels and is able to induce cancer of the colon and prostate. Humans are often exposed to heterocyclic amines due to the consumption of cooked meats, whereby the exposure of those substances ranges from < 1 to 17 ng/kg of body weight per day. There is a challenge to inactivate *E. coli* and at the same time to decrease the formation of heterocyclic amines in heated meats. Recent studies showed that essential oil constituents such as carvacrol which is an active compound of e.g. oregano essential oil is able to reduce *E. coli* as well as heterocyclic amines in cooked ground beef patties. It has been proven that also clove bud essential oils exhibits these dual benefits. This oil showed antimicrobial as well as “anti-heterocyclic-amine” properties. Lemongrass oil exhibits the most effective antimicrobial activity against *E. coli*. The addition of essential oils to uncooked ground beef is able to improve the microbial food safety of heated ground beef patties and to enhance the cancer prevention. [26]

Furthermore, somatic mutations are recognized as an initiating event in the development of sporadic cancers, atherosclerosis and other chronic diseases such as diabetes and neuro-degenerative diseases. The best approach to decrease the incidence of cancer is to avoid contact with carcinogens and mutagens. Many naturally compounds of plant origin such as spices, fruits and vegetables are able to inhibit mutagens and carcinogens, therefore an increasing interest exists to use those substances to prevent mutagenesis and carcinogenesis. There are many papers which describe that essential oils possess a lot of anti-mutagenic activities such as inhibition of mutagen penetration into cells, activation of cell antioxidant enzymes, neutralisation of mutagens by a direct scavenging activity or inactivation of radicals produced by mutagens, inhibition of metabolic conversion of pro-mutagens into mutagens by microsomal enzymes, activation of enzymatic detoxification of mutagens as well as unspecified hepato-protective activity. The essential oil of *Croton regelianus* Müll. Arg. (Euphorbiaceae) was tested for its possible antitumor activity, suggesting an action mechanism similar to that of artemisinin related components. Furthermore, the essential oil of *C. flavens* L. (Euphorbiaceae) was tested for anticancer activity against human lung carcinoma and human colon adenocarcinoma and also the non-mutagenic activity of *C. lechleri* Müll. Arg. bark essential oil was demonstrated. *C. lechleri*, which belongs to the Euphorbiaceae family, is a small-sized Amazonian tree mainly known for its use of sap for which the employment of its stem bark essential oil as a functional food constituent was suggested. In another study, the anti-mutagenetic potential of this essential oil was reported by performing the Ames-test against heterocyclic amines which induce frame-shift mutations. Those heterocyclic amines are well known to be indirect mutation inducers and are produced during cooking of protein rich foods. The Ames-test is a good choice to check the potential chemopreventive role of phyto-complexes. This test is also a good predictive tool for carcinogens. Heterocyclic amines possess a multi-target carcinogen activity and they are related with the development of α- amino-carboniles adducts formation in DNA of cells belonging to stomach, liver, colon, kidney, prostate and skin tissues. Studies have shown that terpenes and their derivatives are potentially useful in the prevention and therapy of several diseases, including cancer. The essential oil constituents from *C. lechleri* such as (+)-limonene and linalool, can inhibit in a dose-dependent manner the development of mammary, liver, skin, lung, colon, prostate, cervical and pancreatic carcinomas. The sesquiterpene β-caryophyllene is claimed to exert an interesting protective capacity against oxidative stress, so this substance is suggested as a promising potential anti-cancerogenic agent. The essential oil of the stem bark of *C. lechleri* was evaluated for its in vitro cytotoxic properties of colon and hepatocellular carcinoma and found that the cytotoxic activity is mainly be determined by the sesquiterpene fractions. Studies have proven that essential oil of *C. lechleri* offers an effective protection against the mutagenic potential of heterocyclic amines with and without metabolic activation and therefore can be used as an additive in foods. This knowledge provides the framework for the development of new anticancer drugs. [27]

Essential oils are also able to inhibit the formation of N-nitroso dimethylamine in vegetables. N-nitroso compounds, such as nitrosamines which are formed by N-nitrosation of secondary amines with nitrite in an acidic environment, act as strong carcinogens. Several foods contain the precursors of this reaction. Meats, cured meat products and smoked fish are sources of secondary amines. Nitrite often occurs in hams and sausages as an antimicrobial or coloring substance. Vegetables are rich in nitrate which is a precursor of nitrite. Crops contain different concentrations of nitrate, dependent on the species, genetic and environmental factors as well as cultivation conditions. There are crops with high amounts of nitrate, such as 1000mg/kg or even more. Whereas, the concentration of nitrite in plants is commonly very low. Especially human saliva is a major source of nitrite. The "Acceptable Daily Intake" of nitrate and nitrite are 3.7 and 0.6 mg. Bacteria in saliva also have an influence on the N-nitroso dimethylamine formation, because they induce the reduction of nitrate. Vegetable foods are the main source of nitrate. Essential oil constituents, such as carvone and limonene, are able to activate the glutathione S-transferase, which reduce the risk of cancer. The terpene hydrocarbon limonene which represents one of the major compounds of citrus essential oils exhibits anticarcinogenic properties against mammary, lung, stomach and skin cancer. It has been reported, that the essential oils of citrus show an inhibitory effect on the formation of N-nitroso dimethylamine. Especially *Citrus junos* Siebold ex Tanaka (Rutaceae), also known as yuzu, which is a popular sour citrus fruit in Japan, shows an inhibitory effect on the formation of N-nitroso dimethylamine. Studies have shown that vegetable extracts exert an inhibitory effect on the formation of N-nitroso dimethylamine in the presence of yuzu oil. Because the Japanese diet is richer in vegetables than in other countries their intake of nitrate is very high and thus have a higher risk to suffer from stomach cancer. Although the rate of formation of nitrosamines is proportional to the square of nitrite concentration, it has been considered, that nitrite in vegetables especially cabbage, celery, spinach and mint is not mainly responsible for the formation of N-nitroso dimethylamine. In most cases oral bacteria are responsible for the reduction of nitrate into nitrite. Terpene hydrocarbons such as myrcene, α-terpinene and terpinolene show an inhibitory effect and cause the decrease of N-nitroso dimethylamine formation. Terpene hydrocarbons compete with dimethylamine to react with nitrite. In conclusion, yuzu oil showed an inhibitory activity on the formation of N-nitroso dimethylamine in the presence of vegetables and saliva. [28]

2.4.9 Essential oils and diabetes

Furthermore, essential oils from different plants can also have a positive effect on diabetes and hypertension. Nowadays, there is a tendency to management type-2 diabetes and hypertension with natural sources. There are two major ways to handle this: The scavenging of free radicals and the inhibition of key enzymes which are involved in starch digestion, such as α-amylase and α-glucosidase. By means of these enzymes starch is converted into glucose which leads to an increase of glucose. Inhibition of these enzymes leads to a delay of the absorption of glucose followed by a moderate postprandial blood glucose elevation. There is also a relationship between diabetes and an increased generation of free radicals as well as a defective antioxidant defense system. Additionally, oxidative stress is involved in the diabetogenic process. For that reason, antioxidant-rich foods have a good dietary intervention in the management of this disease. The use of the essential oil of black pepper seeds in relation with diabetes and hypertension is known in folk medicine. Aromatic spice plants such as black pepper show good antioxidant properties, due to phenolic contents of the essential oil which possesses antimicrobial, anti-hypertensive, anti-convulsive and sedative activities. The essential oil is extracted from the seeds and leaves from black pepper and contains mono- and sesquiterpenes, besides phenolic compounds which are effective in preventing diabetes in animal models. The essential oil of black pepper is established for its radical scavenger abilities and its ferric reducing antioxidant activity, for which especially α-pinene and 1,8-cineole are responsible. The other therapeutic approach is the inhibition of the starch metabolizing enzymes and here the activity of α-glucosidase is stronger inhibited by the essential oil than the one of α-amylase. This circumstance has a therapeutical purpose towards synthetic α-amylase and α-glucosidase inhibitors. The use of those natural products is important in preventing some side effects of the synthetic inhibitors. The essential oil of black pepper can inhibit also the angiotensin-1 converting enzyme (ACE) activity. This fact is a therapeutic approach in the treatment of hypertension which is one of many complications associated with typ-2 diabetes. In vitro the ACE activity was inhibited in a concentration-dependent manner by the essential oil. Therefore, this oil is able to moderate the conversion of angiotensin-1 to the vasoconstrictor angiotensin-2 and thus contributes to the development of hypertension. [29]

Besides the use of essential oil from black pepper also safranal can be used in antidiabetic treatment. The increased activity and expression of protein tyrosine phosphatase 1B (PTP1B) is implicated in the pathogenesis of insulin resistance. 1B (PTP1B) negatively regulates insulin signaling by tyrosine dephosphorylation of insulin receptor. The inhibition of 1B (PTP1B) is anticipated to improve insulin resistance in type 2 diabetics. Saffron which is derived from *Crocus sativus* L. (Iridaceae), is used as spice and in traditional medicine and it inhibits the PTP1B activity on account of its main constituent Safranal. The inactivation of PTP1B results from the covalent modification of the catalytic cysteinyl thiol by safranal by means of a Michael addition. Moreover, an enhanced glucose uptake due to the translocation of glucose transporter 4 was shown by the application of safranal. Insulin resistance of the peripheral tissues and impaired insulin secretion from the pancreas can result in type 2 diabetes mellitus. A general clinical strategy to improve metabolic control in type 2 diabetes is to mitigate the insulin resistance, and inhibition of PTP1B therefore is claimed as a potential therapeutic strategy to treat diabetes. Besides saffron, also other spices such as cinnamon and nutmeg inhibit PTP1B and because of this, these spices are claimed as medicinal foods. This inhibition has been reported to induce a ligand-independent phosphorylation of insulin receptor followed by its downstream signalling. Saffron showed the most remarkable inhibition of PTP1B and the insulin-independent activation of insulin signalling was significantly increased. PTP1B was significantly inactivated with safranal in a concentration-dependent manner. Moreover, an increased level of glucose transporter 4 (GLUT-4) in the plasma membrane fraction was shown by the treatment of safranal. PTP1B specifically dephosphorylates the ubiquitous receptor tyrosine kinase including insulin receptor, insulin-like growth factor-I receptor, nerve growth factor receptor, and epidermal growth factor receptor, and implicating the negative modulation of multiple growth factor signalling pathways. Studies have demonstrated that mice with a lack of PTP1B gene exhibit lower circulating insulin, glucose and triglyceride levels as well as improved insulin sensitivity. Besides, safranal shows also a variety of other pharmacological activities such as antioxidative, hypotensive, antidepressant and anticancer properties and possesses only a very low toxicity upon oral administration. All in all, the use of safranal can be helpful in antidiabetic treatment. [30]

2.4.10 Essential oils and liver disease

Aside from that, essential oils play a big role in the protection against obesity-triggered non-alcoholic fatty liver disease (NAFLD) via modulation of lipid metabolism and oxidative stress. Non-alcoholic fatty liver disease is regarded as the hepatic manifestation of the metabolic syndrome. This disease is the major reason of liver-related morbidity and mortality with an increased prevalence of hyperlipidemia, obesity, insulin resistance and diabetes mellitus. The number of patients with metabolic syndrome is increasing. NAFLD is defined as a fat accumulation in the liver without excessive alcohol consumption. In the worst case it leads to cirrhosis and hepatocellular carcinoma. The inhibition and progression of this morbus is often related to imbalanced lipid metabolism and insulin resistance which induces the accumulation of triglycerides in hepatocytes. Nowadays, there is no specific treatment for NAFLD available. *Allium sativum* L. (Amaryllidaceae) which is commonly consumed as a traditionally food shows a lot of medicinal properties. Garlic essential oil with its major component diallyl sulfide exerts protective activities against the development of NAFLD and health benefits of garlic depend on its antioxidant, antimicrobial, anti-hyperlipidemic, anti-obesity, hepatoprotective and anticancer properties. Garlic essential oils contain more than 30 organosulfur compounds. Diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DATS) are claimed to be the three major compounds. Recent studies have shown that the essential oil from *A. sativum* exerts a positive impact on acute ethanol-induced fatty liver and high-fat induced liver harm based on elevating the antioxidant and detoxification system. However, the underlying effect of garlic essential oil on NAFLD is not clear yet and shows a protective potential against lipid accumulation. Furthermore, the treatment with this essential oil results in an increase in the hepatic GSH level. High fat diet leads to the inhibition of hepatic antioxidant enzymes and this effect is dose-dependently reversed by the application of garlic essential oil. Additionally, the increase of pro-inflammatory cytokines in liver, induced by high fat diet was attenuated this essential oil and oxidative stress and inflammation was decreased as well as HMG-CoA reductase, a protein which regulates cholesterol synthesis. Further, the hepatic PPAR α (peroxisome proliferator-activated receptor*)* and CPT-1(carnitine palmitoyltransferase I) expression levels were up-regulated and the CYP 2E1 expression decreased. As well, the high fat diet induced an increase in hepatic lipogenic protein expression and the decrease of lipolytic protein expression as reversed by treatment of garlic essential oil. NAFLD often results in chronic liver disease and obesity is related to chronic metabolic disorders. The characteristics of metabolic disorders are hyperlipidemia, obesity and insulin resistance. Long term consumption of high fat diet causes typical NAFLD. Studies have shown that garlic essential oil exhibits dose dependent hepatoprotective effects. Moreover, the body weight was lowered, followed by anti-hyperlipidemic effects by reducing serum triglyceride (TG) and total cholesterol (TC) levels. It also furnishes a reduction of free fatty acids which were released by adipose tissue. The key factors of the pathogenesis of NAFLD are imbalanced lipid metabolism and insulin resistance. The clinical indicators of liver function such as aspartat-aminotransferase (AST) and alanin-aminotransferase (ALT) returned to normal levels by application of garlic essential oil. High fat diet renders the liver vulnerable to oxidative stress and toxins which can lead to hepatocyte inflammation. Garlic essential oil enhances the activities of antioxidative enzymes and prevents hepatocyte inflammation by decreasing pro-inflammatory cytokine levels. Hence, this essential oil protects against hepatic oxidative damage resulting from excessive intake of dietary fats. DAS, DADS and DATS, which are the three mayor compounds of garlic essential oil, work synergistically to provide health effects and regulate the detoxification and antioxidant system. It was suggested that DADS is the major active sulfur compound, because DADS was equally effective in preventing obesity and NAFLD as garlic essential oil with the same amount of DADS. Therefore, the essential oil of *A. sativum* and its major active compound DADS are considered as functional food ingredients to prevent NAFLD-related metabolic diseases. [31]

2.4.11 Essential oils and obesity

Essential oils also exert anti-adipogenic activity by suppressing the expression of adipogenic transcription factors. Nowadays, obesity is a major health problem because it is the cause for various diseases such as type II diabetes, cardiovascular disease, osteoarthritis as well as some forms of cancer. Especially the combination of adipogenesis with hypertrophy of adipocytes leads to obesity. Transcription factors regulate the expression of adipogenic genes and the differentiation of adipocytes. The CCAAT/enhancer-binding proteins (C/EBPs are transcriptions factors, which regulate the gene expression from enzymes) and the peroxisome proliferator-activated receptors (PPARs) are the most important transcriptions factors. The differentiation of adipocyte starts with C/EBPb and C/EBPd which induce the expression of C/EBPa and peroxisome proliferator-activated receptor (PPARγ) mRNA. These molecules are able to activate the transcription of adipocyte-specific genes which leads to the generation of functional fat cells. The expression of C/EBPa and PPARγ is also regulated by the extracellular signal-regulated kinases (ERKs), members of the mitogen-activated protein kinases (MAP-Ks). Essential oils from *Acorus calamus* L. (Acoraceae) are often used in the flavouring industry and the production of alcoholic beverages. The major compounds of calamus oil are β-asarone and α-asarone. There are suggestions that β-asarone is able to inhibit the differentiation of 3T3-L1 adipocytes and decreased the expression of PPARγ, C/EBPa and C/EBPb, as well as the phosphorylation of p-ERK in 3T3-L1 cells. [32]

2.4.12 Essential oils and mood disorders

Furthermore, some essential oil constituents, such as (E)-methyl isoeugenol (MIE) is often used as food flavour. This essential oil from *Pimenta pseudocaryophyllus* (Gomes) L.R. Landrum (Myrtaceae) leaf has calming properties. This ubiquitous food additive appears attractive for treatment of mood disorders. Studies demonstrated the anxiolytic and antidepressant like activities of MIE, suggesting the participation of serotonergic pathways. Among psychiatric diseases mood disorders are most common, namely widespread with a prevalence of up to 20 % worldwide. Because of the low remission rate and the high rate of non-response to current treatment, it is

necessary to develop new therapeutic agents, such as consumption of functional food. With this basic food nourishment health benefits are covered as well. For as long as anyone can remember, plants are used as medicine and food. Traditional foods show health effects based on specific pharmacological effects of plants. Today, aromatic plants have been largely explored as functional ingredients in the pharmaceutical as well as in the food industry. The treatment of neural disorders with naturally occurring food flavours, such as MIE, seems to be more acceptable than the use of pharmacotherapies. Oral administration of MIE showed an increase in sleep duration and a depressive activity of the CNS. Anti-seizure property of MIE was hypothesized, because it is a central nervous system depressive compound like diazepam. This hypothesis is supported by the anti-seizure property of aromatic compounds such as methyleugenol, eugenol and 1-nitro-2-phenylethane which have similar chemical structure as MIE. Studies showed anxiolytic and antidepressive like properties of this essential oil constituent, suggesting the participation of serotonergic pathways. [33]
Besides MIE, the essential oil of lemon which is widely consumed in the diet, are also known for their antidepressant-like effect and therefore acts as functional food ingredient. Because of many side effects using conventional pharmacotherapy against depression, such as nausea and anorexia, there is a growing interest in the search of new effective antidepressants, such as functional foods, e.g. lemon which is used worldwide in the kitchen. The oral administration of lemon essential oil does not show any toxic effect or influence on the weight, blood and organs of rodents. Upon oral administration of 400 mg/kg lemon essential oil the dopaminergic activity in the striatum and the hippocampus was significantly enhanced on account of an increased concentration of dopamine and a decreased turnover of it. It is known, that depressed patients have a dysfunctional 5-hydroxytryptamin (5-HT) system. Selective 5-HT-re-uptake inhibitors enhance the activation of various 5-HT receptor subtypes. In conclusion, the essential oil of lemon has

a great potential to be used as an antidepressant functional food ingredient. [34]

2.4.13 Essential oils and infertility

Essential oils can also be useful for astheno-zoospermic men. Men infertility is a major health problem because the structure of lipid matrix in the membranes of spermatozoa, which contains a lot of polyunsaturated fatty acids (PUFAs), can be destroyed by lipid peroxidation. Reactive oxygen species belong to the class of free radicals which are produced in various organs, including the testis. This can lead to the loss of motility and to the defect of membrane integrity of the spermatozoa. The application of ROS scavengers, therefore improves sperm function. Cinnamon is well known as spice and herbal medicine on account of its high content of eugenol but the principal bioactive compound is cinnamaldehyde. Cinnamom is famous for its antibacterial, antifungal, antiviral, anti-inflammatory, anti-neoplastic, anti-hyperglycaemic and anti-hyperlipidaemic activities. Studies have shown that cinnamon bark has a positive effect on sperm quality, LH, FSH, and testosterone concentrations. Cinnamon bark oil administration caused a significant decrease in the concentration of malonic dialdehyde and an increase of glutathione, compared with the control group. The primary constituent in the bark oil is cinnamaldehyde and the major compound of cinnamon leave oil is eugenol. It has been reported that the use of cinnamon bark oil significantly increases the weight of testes. The increased weights of testes probably stems from the increased testosterone concentration which is important for the development, growth and normal function of the testes and male accessory reproductive glands. Moreover, an increase in sperm concentration was noted. ROS are normally produced in metabolic processes, but when ROS were excessive produced by spermatozoa it leads to the formation of toxic lipid peroxides. Their antioxidative enzymes are used as defense mechanism of cells against an accumulation of ROS. Choline acetyltransferase (CAT) and glutathion (GSH) are claimed as the main detoxifying systems for peroxides. Recent studies showed a significant decrease in malonic dialdehyde (MDA) level, which is a byproduct of lipid peroxidation (LPO), as well as an obvious increases in reduced glutathione (rGSH) level, glutathione peroxidase (GSH-Px) and CAT activities in testicular tissue by the consumption of cinnamon bark oil. ROS can react with a lot of intracellular molecules, especially PUFAs (phospholipids, glycolipids, glycerides and sterols) and trans-membrane proteins with oxidizable amino acids. In an autocatalytic process ROS can attack the unsaturated bonds of the membrane lipids, thus furnishing the production of peroxides, alcohol and lipidic aldehydes as byproducts of the reaction. Spermatozoa are especially susceptible to peroxidative damage, because of their high amount of PUFAs which are involved in sperm maturation as well as in spermatogenesis. The structure of lipid matrix in the membranes of spermatozoa is destroyed by the peroxidation of sperm lipids. These results in decreased sperm viability and increased morphological midpiece and in extreme cases it can completely inhibit spermatogenesis. It has been shown that the consumption of *C. zeylanicum* leads to a significant increase in sperm motility and an increased sperm concentration. Cinnamon bark oil leads to the improvement of sperm quality which can be linked with LPO. All in all, long term consumption of cinnamon bark oil results in an improved sperm quality and a tendency to decrease apoptotic germ cells which is related with the decrease of testicular LPO and increased antioxidant enzyme activities. [35]

2.4.14 Essential oils and osteoporosis

Furthermore, essential oils can also be useful in the treatment of osteoporosis. This disease is a major health problem in aging humans when low bone mass leads to osteoporotic fractures. Osteoporosis is much more frequent in women. The bone turnover is increasing, especially after the menopause. This leads to a marked decrease in trabecular bone mineral density (BMD) and bone mineral content (BMC). Osteoporotic fractures reduce the quality of life of the patient and they are a burden to health care. Hence, it is desirable from a medical as well as from an economical view to prevent the loss of bone mass. A nutritional approach would be an inexpensive opportunity to prevent low bone mass. Studies have shown that essential oils from sage, rosemary and thyme as well as essential oils from pine, juniper and eucalyptus inhibit or at least retard the activity of osteoclasts. The essential oil of pine is the most potent one and also bitter orange-peel oil is very potent, for which monoterpenes, such as thujone, eucalyptol, camphor, borneol, menthol and thymol are responsible. Studies have shown that pine oil reduces the loss of trabecular BMD in animal models and in vitro studies report that monterpenes such as borneol, thymol, and camphor inhibit directly osteoclast activity. Hence, this suggests that those essential oil constituents inhibit bone resorption by acting directly on bone cells whereas others act only indirectly, such as by influencing calciotropic hormones or via stimulation of the intestinal calcium absorption. Studies have demonstrated, that menthol, which is the most widely used monoterpene in human nutrition, inhibits bone resorption in vivo and in vitro, but the latter effect is weak. [36]

It has also been reported that the consumption of fruit and vegetables is linked with a greater bone mineral density in humans. Animal studies have shown that vegetables, salads and herbs, which are part of human nutrition, are able to inhibit bone resorption. Monoterpenes, mostly the major components of essential oils, are present in several herbs which are commonly used in human diet. Essential oils have a positive effect on bone metabolism when they are added to food of rats. Therefore, those herbs which contain essential oils can be possible candidates for a dietary approach to osteoporosis. The presence of the above mentioned monoterpenes which exert inhibitory effects in vivo, but not in vitro, leads to the hypothesis that those substances are metabolized to active compounds in vivo. For example cis-verbenol as a metabolite of α-pinene inhibits the osteoclastic resorption activity. Monoterpenes might inhibit the mevalonate pathway and the prenylation of small G-proteins such as Ras (rat sarcoma), Rho and Rac which results in the inhibition of these signaling proteins. Monoterpenes are known for their high hydrophobicity, therefore they are able to incorporate themselves into cell membranes and affect cell functions. This inhibiting effect was observed in murine models. [37]

2.4.15 Essential oils and their effect on the gastrointestinal tract

Essential oils are also famous for their positive effect on the gastrointestinal tract. *Mentha x piperita* L., (Lamiaceae) contains a volatile oil with the major compound (1R,3R,4S) (-)-menthol. This essential oil is used against irritable bowel syndrome, because of its influence on gastric motility. The oil is also known for its carminative, cholagogue and sedative effect. Peppermint tea is commonly used against acute and chronic gastritis, enteritis and disturbances of the GI-tract by its antispasmodic effect of menthol. This effect is partly based on the Ca^{2+}-channel modification. (-)-Menthol, menthon and similar compounds are able to modulate the ionotropic channels of $GABA_A$- and glycine receptors stereoselectively. Furthermore, peppermint tea is commonly used as an antiemetic, which is a remedy in pregnant women besides ginger and cannabis. This volatile oil shows the same effect as 5-HT_3-receptor antagonists, 5-HT_4-receptor agonists and anticholinergics. Those receptors are also involved in the pathogenesis of irritable bowel syndrome. Peppermint oil as well as (-)-menthol are able to completely inhibit 5-HT_3-receptor in a concentration dependent manner by relaxing the smooth muscle and antagonizing the serotonin-induced stimulation. This antagonistic effect on the 5-HT_3-receptor channel influences in a positive manner the disturbed motility during symptoms of irritable bowel syndrome and emesis. The cationic influx through 5-HT_3-receptor channels was inhibited by peppermint oil and its main constituent (-)-menthol. They do not act directly, because they do not compete with the radioligand for the 5-HT_3-binding site. The influence of peppermint essential oil and (-)-menthol leads to the reduction of serotonin-induced contraction in animal models. In addition, this oil possesses direct relaxant effect. [38]

Essential oils often are used as food additives to complement present therapies of gastritis and peptic ulcers. This disease is caused by an increased density of *Heliobacter pylori* in the gastric mucosa. A nutritional approach can help people with asymptomatic gastritis to manage the infection and to decrease the development of the disease. Those essential oils which exhibit the strongest bactericidal potential against *H. pylori* P1 were also active against other *Heliobacter* strains. The most effective single essential oil constituents against *H. pylori* are carvacrol, isoeugenol, nerol, citral, and sabinene. The widespread infection with *H. pylori* is well known as the major etiological factor in chronic active type B gastritis, gastric ulcers and gastric cancer. Nowadays, a triple therapy such as the combination of proton-pump inhibitor and two antibiotics are common. Antibiotic resistance is responsible for eradication treatment failure. Therefore, there is a growing interest to find alternative treatments, e.g. the development of a vaccine approach to stimulate the host immune defense or the development of new nutritional approaches. Especially patients with asymptomatic gastritis profit from the nutritional approach. As mentioned above, essential oils are well known for their antimicrobial properties, but not all of them are able to kill all bacteria. Essential oils are more effective against *H. pylori* at acidic pH. [39]

2.4.16 Essential oils and immunmodulatory activities

Essential oils are also known for their immunmodulatory activity. (+)-Limonene, which is a cyclic monoterpene, is a major compound of several essential oils and because of its sweet, citrus-like fragrance it is often used in the food and beverages as well as in perfumes as additive. This essential oil constituent occurs in several fruits such as orange, lemon, mandarin, lime and grapefruit. (+)-Limonene also has an effect on the immune system function, especially on T-lymphocytes in that it increases the total antibody production and bone marrow cellularity. (+)-Limonene is also able to suppress or enhance lymphocyte proliferation and specific antibody responses. Additionally, the treatment with (+)-limonene leads to an increased production of nitric oxide, phagocytic activity and microbicidal activity of macrophages in lymphoma-bearing mice and at the same time to the inhibition of lymphocyte proliferation at high doses. The results of in vitro studies showed that (+)-limonene suppresses the lipopolysaccharide induced production of nitric oxide, prostaglandin E_2 and proinflammatory cytokines, whereas the Ras/MAP kinase driven production of IL-2 by purified human T-lymphocytes was inhibited by perillic acid. (+)-Limonene is rapidly metabolized to oxygenated metabolites, such as perillic acid and limonene-1,2-diol and they all inhibit the production by CD3+ CD4+ T-cells of IFN-γ, IL-2, TNF-α, IL-4 and IL-13, and the production by CD3+ CD8+ T-cells of IFN-γ, IL-2, and TNF-α. Moreover, the up-regulation of CD25, CD69 and CD40 by activated T-lymphocytes are modulated. High concentrations of those substances induce T-lymphocyte cell death. (+)-Limonene is able to enhance or inhibit the proinflammatory activity of macrophages and the proliferation of lymphocytes. Variations in the in vivo models and the dose of (+)-limonene might be responsible for these contradictory results. The production of TH1 and TH2 cytokines by CD4+ and CD8+ cells is significantly inhibited by the treatment with (+)-

limonene. Additionally, limonene-1,2-diol and perillic acid, also suppress the production of proinflammatory cytokines leading to the suggestion that the in vivo application of (+)-limonene may have immunosuppressive effects. Another study has shown that the treatment of (+)-limonene leads to an increase of the total antibody production, which might be a by-product of the increased total white blood cell count. By the inhibition of the production of TH2 cytokines, such as IL-4, (+)-limonene is probably able to impede the proliferation and differentiation of B-lymphocytes. Furthermore, it inhibits antibody affinity maturation and class switching which results in an impaired humoral response. The inhibition of the TH1 cytokines INF γ and IL-2 as well as of CD25 expression which is a cell surface molecule plays a big role in the clonal expansion of T-cells. (+)-Limonene as well as its metabolites might impair the activity of cytotoxic T-cells which are involved in immune surveillance. (+)-Limonene can also act as an agonist for the adenosine A_{2A}-receptor which has widespread anti-inflammatory effects, such as the inhibition of pro-inflammatory cytokine production and proliferation of T-lymphocytes. The anti-inflammatory activity of (+)-limonene is independent from the adenosine A_{2A}-receptor activation and has the GRAS status for use as a flavouring agent. The therapeutic window of the substance must be watched carefully, in order to prevent adverse cytotoxic side effects. The average daily intake of (+)-limonene via dietary in the U.S. is estimated to be 16.2 mg. (+)-Limonene is almost completely absorbed in the gastrointestinal tract through oral application and is rapidly distributed to various tissues in the body, such as blood serum, liver, lungs and so on. [40]

2.4.17 Essential oils and Alzheimer´s disease

Essential oils can also be used in the treatment of Alzheimer´s disease. This disease depicts the most common cause of dementia in the aged population. It results in cognitive decline and mental deterioration which is the result of a massive and progressive loss of neurons from different regions of the brain [41]. At the synaptic gape the neurotransmitter choline is released. Disorders of the CNS are linked with neurotransmitter disturbances and insufficiencies in cholinergic functions. Cholinesterase is responsible for the hydrolysation of choline and if there is a high concentration of this enzyme, than a lower concentration of choline in the synaptic gap is the result. Investigations have shown that there is a relation between increased levels of cholinesterase enzymes and Alzheimer´s disease. This fact leads to the hypothesis that the cognitive decline in patients is linked to the progressive cholinergic degeneration. Hence, promising approaches for the treatment of Alzheimer´s disease are cholinesterase inhibitors, which are able to enhance the level of cholinergic neurotransmitters in the brain. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are the major cholinesterase enzymes, which are responsible for the decreasing choline levels. Today Alzheimer´s disease patients are treated with AChE inhibitors such as Donepezil® and Galantamine® as well as the AChE- and cholinesterase co-inhibitor Rivastigmine®. AChE and BChE inhibitors are synthetic compounds, which reveal some toxicity during prolonged use. Hence, there is a great demand for alternative drugs to treat Alzheimer´s disease. [42] It has been suggested that dietary supplements with antioxidants and free radical-scavengers may decrease the mild cognitive impairment of Alzheimers disease. [41] A high amount of plants have been traditionally used for the enhancement of cognitive function as well as to alleviate several symptoms linked with Alzheimer´s disease. Nowadays, essential oils of edible plants are considered to inhibit AChE and BChE. Those volatile oils are of great interest, because of their availability, few side effects, low toxicity and their biodegradability. Studies have demonstrated that the essential oils of *Citrus aurantifolia* (Christm.) Swingle (Rutaceae), *Alpinia galanga* (L.) Willd. (Zingiberaceae) and *Melissa officinalis* L. (Lamiaceae), possess the highest inhibitory activity against AChE whereas *M. officinalis*, *C. aurantifolia* and *Ocimum gratissimum* L. (Lamiaceae) showed the strongest inhibitory properties against BChE. Therefore, the essential oil of *C. aurantifolia* is a promise for the prevention and treatment of Alzheimer´s disease, because it inhibits both enzymes. The major constituents of *C. aurantifolia* leaf essential oil are (+)-limonene, (-)-camphor, citronellol, ocimene and 1,8-cineole. 1,8-cineole, which is one of the most potent AChE inhibitors also occurs in other plant such as *Rosmarinus officinalis* L. (Lamiaceae). [42]

2.4.18 Essential oils against food browning

Furthermore, essential oils are also effective in the inhibition of tyrosinase which is useful for applications in food technology. Tyrosinase is a widely distributed copper-containing enzyme which is present in fungi, higher plants and animals. [43] It contains three domains, whereas the central domain exhibit two copper binding sites which are the active site in the tyrosinase catalytic reaction. [44] This enzyme is involved in the melanin pathway. Tyrosinase catalyses the hydroxylation of L-tyrosine to L-3,4-dihydroxy phenylalanine (L-DOPA) and the oxidation of L-DOPA to o-quinone. Cyclization of DOPA-quinone and oxidative polymerization of the resultant indoles are involved in the generation of melanin pigments. Tyrosinase can lead to browning of fruits and vegetables by oxidizing a variety of phenolic compounds, resulting in a decrease in nutritional quality and market value of food products. For the treatment of hyperpigmentation disorders, the lightening capability was tested of several chemicals. A large amount of anti-food-browning agents are based on the inhibition of tyrosinase activity, because this enzyme catalyzes the key steps of melanin biosynthesis. Compounds, which are used for their anti-melanogenic activity in food processing often do not satisfy high clinical efficacy, selectivity, low toxicity and chemical stability. Therefore, natural tyrosinase inhibitors of herbal origin which are considered to be safer as synthetic ones are wanted. Essential oils from lavender and peppermint exert an anti-melanogenic potential, so they can be used as additives in food products. The essential oil of lavender mainly consists of the terpene alcohol linalool and its ester linalylacetate whereas the major compounds of peppermint volatile oil are the monoterpenoid ketone piperitenone oxide, the bicyclic ether 1,8-cineole, limonene and the linear monoterpene myrcene. But none of these major compounds of either peppermint or lavender oil have shown any anti-tyrosinase effects, except myrcene which was isolated from citrus essential oils. Hence, it is considered that the anti-tyrosinase activity of these essential oils is the result of a synergism with their different components. Both oils show a dose-dependent inhibitory effect on tyrosinase, the essential oil from lavender inhibits the enzyme non-competitively, whereas peppermint oil is active by a mixed inhibition mechanism. [43]

As mentioned above, also essential oils from the citrus group show inhibition of tyrosinase. Those essential oils which are rich in sabinene, citral, neryl acetate, geranyl acetate and myrcene inhibit the oxidation of L-DOPA by tyrosinase. Sabinene, neryl acetate, and geranyl acetate only show an effect at high concentrations. Thus, citral and myrcene must be responsible for the inhibitory activity. In several essential oils geranial (the trans isomer of citral) occurs in a higher concentration than the cis isomer, neral. It has been reported that geranial is more effective in inhibition of tyrosinase activity than neral. In another citrus essential oil myrcene is the most abundant compound which is responsible for this inhibitory effect as well. [44]

Natural essential oils can also be used to reduce the peroxidase activity in leafy vegetables. Polyphenol oxidase and peroxidase can lead to enzymatic browning in fruit and vegetables during storage. Both enzymes are not only responsible for browning of foods, but also lead to discoloration, off-flavours as well as nutritional damage. Peroxidase is able to interact with hydrogen peroxide which results in an activated complex which reacts with a donor molecule. Therefore, it is necessary to inactivate the peroxidase enzyme to minimize the deterioration. These enzymes are normally inhibited by heath, a low pH or by means of adding chemical additives. Although heating is an effective way to inactivate enzymes it leads to thermal damage of nutritional and sensory quality and consumers prefer minimally processed fruits and vegetables without the loss of quality attributes, thus alternative anti-browning compounds are of great interest. Essential oils from clove, rosemary, lemon, melissa and tea tree show high antioxidant properties and possess the potential to be used as sanitizing agents. The antioxidant effects of essential oils were lower compared to synthetic ascorbic acid, but they provide other benefits such as prophylactic agents for human diseases. [45]

2.4.19 Essential oils and anti-inflammatory activities

The essential oil constituent such as (E)-β-caryophyllene is known for its anti-inflammatory properties and is commonly consumed by vegetable food. Inflammatory as well as other pathophysiological processes are modulated by a daily intake of about 10-200 mg of this lipophilic sesquiterpene by the endocannabinoid system. This sesquiterpene is a functional non-psychoactive cannabinoid receptor type 2 (CB_2) ligand, which occurs in food. By activating CB_2-receptor, inflammation, pain, atherosclerosis and osteoporosis can be treated. The widespread (E)-β-caryophyllene selectively binds to the CB_2-receptor and acts as an agonist. The binding of (E)-β-caryophyllene to the cannabinoid receptor type 2 causes a lot of reactions such as inhibiting adenylate cyclase which leads to intracellular calcium transients and weakly activates the mitogen-activated kinases Erk1/2 and p38 in primary human monocytes. Furthermore, lipopolysaccharide (LPS) induced proinflammatory cytokine expression in peripheral blood was inhibited by (E)-β-caryophyllene. Additionally, the LPS-stimulated Erk1/2 and JNK1/2 phosphorylation in monocytes was attenuated by this essential oil compound. Several different food and spice plants such as oregano, cinnamon and black pepper contain this sequiterpene which is used as food additive because of its aromatic taste. It has been reported that ligands of the CB_2-receptor inhibit inflammation as well as edema formation. Moreover, those ligands exhibit analgesic effects and play a protective role in hepatic ischemia-reperfusion injury. Furthermore, CB_2-receptor agonists have a positive effect on the gastrointestinal helping to prevent colitis by inducing inflammation. The CB_2-receptor also depicts a potential target for the treatment of atherosclerosis and osteoporosis. CB_2-receptor agonists exert an inhibition of LPS-stimulated TNF-α and IL-1β expression maybe through a CB_2-receptor-mediated suppression of Erk1/2 and JNK1/2 signalling. [46]

2.4.20 Essential oils and menstrual pain

Cinnamaldehyde, the major active compound of cinnamon bark offers a great potential to treat menstrual pain and infertility. [47] Cinnamon is one of the oldest spices, which is available in two forms- the cinnamon stick or cinnamon powder. Cinnamon is an evergreen tree, native to the Lauraceae family and famous for various health benefits. The characteristic taste of cinnamon results from cinnamaldehyde which is aging in the presence of oxygen. [48] Menstrually-related migraine is linked with progesterone levels. It has been shown that menstrual distress is associated with higher levels of estradiol and higher estradiol/progesterone levels. Cinnamaldehyde, the major compound of cinnamon, is able to stimulate dose-dependently the production of progesterone in adrenocortical cells, whereas the concentration of testosterone and dehydroepiandrosterone release was decreased. The administration of exogenous intrauterine progesterone is able to reduce dysmenorrhea and to lower prostaglandin $F_{2\alpha}$ content of menstrual blood in dysmenorrheic women. There is a relation between arachidonic acid metabolites in menstrual fluid and menstrual pain and the formation of eicosanoids is decreased by hormonal contraceptives. There are further in vivo studies necessary, whether the progesterone-release by cinnamaldehyde leads to therapeutic effects such as hormonal contraceptives.

2.4.21 Essential oils and atherosclerosis

The essential oil of sage can be used as food ingredient with anti-inflammatory and anti-atherogenic properties. Cholesterol deposition in the intima of large and medium size arteries together with a chronic inflammatory process leads to atherosclerosis. Oxidized low density lipoproteins play a key role in early inflammation. This type of LDL, which is not recognized by the LDL receptor is taken up by the scavenger receptors in monocytes-macrophages and endothelial cells. Hence, this leads to an accumulation of cholesterol in macrophages and to the formation of foaming cells. Moreover, oxidized LDL is able to induce the expression of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 in macrophages and endothelial cells. Essential oils from spices which are added to food, present various biological activities, such as antioxidant, anti-inflammatory properties and so on. It has been reported that *Salvia officinalis* L. (Lamiaceae), exert anti-inflammatory properties. The essential oil of salvia is able to inhibit COX-2. As mentioned above, the oxidation of LDL results in atherosclerotic lesion and the initiation of the inflammatory cascade. IL-1β and TNF-α play an important role in the initial amplification of the inflammatory response. Moreover, they are able to induce the expression of adhesion molecules by endothelial cells and promote secretion of different cytokines and chemokines by monocytes. Furthermore, they are involved in the process of foam cell formation, especially via the induction of grown factors. Activated macrophages, lymphocytes, fibroblasts, and vascular smooth muscle cells, produce during stimulation by IL-1 and TNF-α the secondary inflammatory cytokine IL-6. This cytokine plays an important role in the development and progression of atherosclerosis. Studies showed that supercritical *S. officinalis* extracts are effective inhibitors of oxidized LDL induced pro-inflammatory cytokines. Only small doses of supercritical sage extracts are able to prevent cytokine stimulation. Supercritical sage extract mainly consists of camphor, borneol and 1,8-cineole which is a strong inhibitor of TNF-α, IL-1β and IL-6 production. Borneol and camphor also exhibit excellent anti-inflammatory properties. Therefore, sage extract possesses a great potential to be used as an anti-inflammatory agent to prevent atherosclerosis. [49]

Moreover, essential oils can help to prevent cardiac disease mortality. Low-density lipoproteins (LDL) mainly consist of polyunsaturated fatty acids. As mentioned above, the oxidation of LDL can result in atherosclerosis. Permanent oxidation results in the generation of foam cells and plaque, which are the symptoms of atherosclerosis. It has been reported, that diets which are rich in vegetables and fruits exhibit lower rates of coronary heart disease and cancer. The occurrence of chronical heart disease is reduced by the consumption of phenolic antioxidants in food. The antioxidant activity of essential oils is related to the total phenol compounds. The total phenol content is dependent on several factors such as plant variety, location, growing factors, extraction techniques and so on. Clove, eugenol basil and and red spanish showed the highest total phenol concentration. The antioxidant activity of essential oils these can differ dependently on the plant varieties which are used. If eugenol is the major compound of the essential oil the inhibition rate of LDL oxidation is ranged between 68 % and 100 %. On the other hand, essential oils which contain methylchavicol, anethol, p-cymene, apiol and cinnamic ether inhibit LDL oxidation less than 2 %. Essential oils like thymol and carvacrol exert intermediary activity against LDL oxidation. [50]

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