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EXTRACTION DESIGNS AND THERAPEUTIC ATTRIBUTES ASSOCIATED WITH LIMONENE: A REVIEW

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ABSTRACT

Citrus rinds contain a tremendous amount of essential oils. The peels contain majority of the essential oils that are continuously wasted. One of the major constituents of the essential oils in the zest of different citrus fruits like orange, tangerine, lemon and grapefruit is limonene. The review aims at discussing various conventional and novel extraction methods of limonene from citrus fruits. The review also discusses various therapeutic properties of limonene and the mechanism behind these properties. Limitations in the use of limonene such as toxicity and side-effects will be delineated. Limonene is present in the range of 26.9-97.83% in the citrus essential oils. The percentage of limonene in the essential oil depends on the *Citrus* species and extraction methodology. There are different extraction methods such as hydrodistillation, steam distillation, cold pressing, microwave-assisted extraction, ultrasound sound assisted extraction and supercritical fluid extraction. Various therapeutic potential of limonene has been reported. Limonene is usually non-toxic but its epoxides can be toxic at the very high dose. This up to date and comprehensive review aims to provide a valuable overview of limonene and its therapeutic potential.
Keywords **:** Limonene, Extraction, Anticancer, Pharmacological activity, Commercial use, Citrus

Introduction

Citrus fruits such as orange, tangerine, lemon, grape fruit, and lime belonging to the family Rutaceae are one of the most cultivated fruits throughout the world (Raimondo *et al*., 2018). Annually 31.2 million tons of citrus fruits are processed globally and a huge amount of waste (almost 110-120 million tons) is produced after the processing is done both at the small scale as well as the industrial level (Mahato *et al*., 2020; Sharma *et al*., 2017). The calculated amount of citrus waste in Korea was estimated as sixty thousand tons per year(Mahato *et al*., 2017). The edible part as well as the peels are rich indifferent chemical compounds like phytochemicals, phenolics, vitamins and essential oil contents (Mahato *et al*., 2017; Mazur-Marzec *et al*., 2018). The major essential oil reported in the citrus peels is the limonene. The citrus fruit peels differ not only in color and surface properties but also in the limonene content. The outer skin known as zest contains maximum limonene. The limonene exists in two optical isomeric forms namely D-limonene and L-limonene (Review, 2020). The D-form of the limonene is more abundant in citrus fruits peel essential oils than the L-formwhereas L-limonene is more abundant in *Mentha*species (Duetz *et al*., 2003). It is a volatile monoterpene used as a flavoring agent and a preservative (Atti-Santos *et al*., 2005). The ubiquitous colorless and 10 carbon compound is found in numerous other plant genera such as *Lippia*, *Artemisia*(sagewort) and *Cannabis* also (Fraternale *et al*., 2015; Gómez *et al*., 2013; Gurgel do Vale *et al*., 2002; Khan *et al*., 2012; Menezes *et al*., 2014; Russo, 2011; Zhou *et al*., 2019). Limonene has been found to show herbicide properties and acts as an attraction for pollinators (Erasto & Viljoen, 2008). This review explains the different methodologies which can be used in the extraction of the limonene. The methods like solvent extraction, steam distillation with cold press and hydro distillation using Clevenger system are very effective in its easy isolation (Ramgopal *et al*., 2016). The extraction accuracy depends on the maintenance of the static temperature and condensation without allowing citrus pomaces to burn (Davidowski, n.d.). The validated GC-MS instrument can be used to analyze and quantify the percentage purity of the limonene (Son *et al*., 2018). The different therapeutic properties of the limonene have been analyzed in this review comprehensively. The anti-cancer activity shown by the limonene is in the form of cell cycle arrest and activation of pro apoptotic genes. The gall stone dissolution by limonene is also studied in relation to its purity and its effect on activity of gastric acid. The challenges that the researchers are facing in the use of antibiotics is the development of drug resistance mechanisms that have evolved in various microbial strains like methicillin and triclosan resistance against *Staphylococcus aureus* and *Pseudomonas aeruginosa* respectively (White & Mcdermott, 2001). The emergence of drug resistance in different pathogenic fungi is also an emerging public health concern (Cortegiani *et al*., 2019). To overcome these issues researchers see limonene as the eco-friendly natural components that is feasible against these microbial strains. Researches have confirmed (+)-limonene having the bacteriostatic, bactericidal and anti-fungal properties. In *Escherichia coli* BJ4 it does so by causing the cell permealization which is analyzed by fluorescence microscope and also the microbial inactivation when used in association with pulsed electric fields (Espina *et al*., 2013; Ramgopal *et al*., 2016). In evaluating its anti-fungal activities the volatile vapor of limonene has shown fungi static and fungicidal activity against *Trichophyton rubrum,* the most common causative agent nail infections in human (Chee *et al*., 2009). While in yeast, like*, Kloeckera apiculata, Rhodotorulaglutinis, Candidabolmii* t he lowest D-limonene concentration has been found to have better anti-fungal activity that of the standard antibiotics(Ünal *et al*., 2012).

Essential oils

Plants as well as fruits are known to produce enormous number of chemical metabolites. These metabolites may be categorized into primary (amino acids, nucleic acids, lipids and sugars) and secondary metabolites. The secondary metabolites may or may not be required for the growth but they certainly provide protection against pathogenic microbes, insects, and herbivores. There are around 374,000 plant species and more than 100,000 phytochemicals (Christenhusz & Byng, 2016; Leitzmann, 2016). The secondary metabolites are also plant products and are categorized into alkaloids (1200 types), terpenes/terpenoids (25000 types) and phenolic compounds (8000 types).The terpenes/terpenoids include the essential oils and almost all of them are odiferous and volatile in nature. In plants they are generally produced in the leaf chloroplast(Hamid *et al*., 2011). The essential oils can be extracted from different plant parts such as flowers, bark, stem, fruits and leaves (Ali *et al*., 2015). They provide plant protection from bacteria, fungi, and insects; and also help in repelling herbivorous animals (Bakkali & Idaomar, 2008). Essential oils known for their enormous biological activities are made up of different chemical components. However, the major components include; hydrocarbon, phenol, aldehyde, alcohols, ketones and esters. These include the oxygenated compounds and are defined as, "volatile materials of odorous plant origin which are derivatives of oxygenated terpenes such as aldehydes, ketones, phenols, and alcohols (Rassem *et al*., 2016). The major components of essential oils from different plants and their sources have been listed in Table 1. From the essential oils of *Citrus* species more than one thousand compounds have been isolated(González-Mas *et al*., 2019) [30].Although hundreds of compounds have been reported from the citrus oils, the major component of the citrus essential oil is limonene (Ben Hsouna *et al*., 2017; González-Mas *et al*., 2019; Jing *et al*., 2014; Velázquez-Nuñez *et al*., 2013). In citrus rind essential oils the concentration of limonene ranges between 60-95% of the oils (González-Mas *et al*., 2019). The concentration of limonene in the citrus essential oils from different Citrus species is listed in Table 2. The table shows varying concentration of limonene in the citrus essential oils extracted from same species such as *Citrus aurantium* and *Citrus sinensis.* The composition of essential oils is affected by geographical distribution and various environmental factors such as temperature, sunshine duration and altitude(Ben Hsouna *et al*., 2017).

Table 1: Major essential oil components of some plants.

Major Essential OilComponents	Source	Reference
Pinene	*Cuminum cyminum, Piper nigrum*	(Salehi *et al*., 2019)
Virdiflurol	*Melaleuca quinquenerria*	(Padovan *et al*., 2010)
Sabinene	*Myristica fragrans*	(Ogunwande *et al*., 2013)
Globulol	*Eucalyptus globulus*	(Tan *et al*., 2008)
Terpinolene	*Pastinaca sativa*	(Russo & Marcu, 2017)
Limonene	Citrus fruits	(Jongedijk *et al*., 2016)
Cineole	*Eucalyptus globulus*	(Aprotosoaie *et al*., 2018)
p-Cymene	*Cuminum cyminun, Thymus vulgaris*	(Bagamboula *et al*., 2004; Ravi *et al*., 2013)

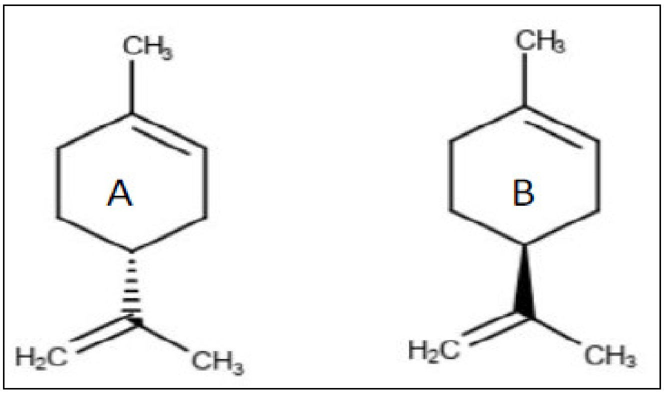
Table 2 : The concentration of limonene in the essential oils from different *Citrus* species.

Limonene percentage in citrus essential oils	Citrus species	Part	Source country	Reference
74-86%	*Citrus aurantium*	Pericarp	USA	(Nunes Wolffenbuttel *et al*., 2015)
94.27%	*Citrus aurantium*	Pericarp	Italy	(Caccioni *et al*., 1998)
97.83%	*Citrus aurantium*	Pericarp	Brazil	(De Moraes Pultrini *et al*., 2006)
83-97%	*Citrus sinensis*	Pericarp	USA	(Nunes Wolffenbuttel *et al*., 2015)
91.14-94.95%	*Citrus sinensis*	Pericarp	Italy	(Caccioni *et al*., 1998)
91.63-92.57%	*Citrus sinensis*	Pericarp	Colombia	(Blanco Tirado *et al*., 1995)
90.68%	*Citrus sinensis*	Pericarp	Korea	(Choi, 2003)
78.5%	*Citrus sinensis*	Pericarp	Algeria	(Ferhat *et al*., 2006)
90.66%	*Citrus sinensis*	Pericarp	India	(Singh *et al*., 2010)
46.7%	*Citrus reticulate*	Pericarp	India	(Chutia *et al*., 2009)
39.74%	*Citrus limon*	Flowers	Tunisia	(Ben Hsouna *et al*., 2017)
89.96%	*Citrus grandis*	Pericarp	China	(Tao & Liu, 2012)
93.33%	*Citrus paradise*	Not available	Japan	(Deng *et al*., 2020)[51]
47.5-48.9%	*Citrus latifolia*	Pericarp	Brazil	(Atti-Santos *et al*., 2005)
77.27-79.36%	*Citrus volkameriana*	Pericarp	Colombia	(Blanco Tirado *et al*., 1995)
45.36%	*Citrus medica*	Not available	China	(Li *et al*., 2019)
91.27%	*Citrus deliciosa*	Pericarp	Brazil	(Dias *et al*., 2020)
95.77%	*Citrus monstruosa*	Pericarp	Italy	(Flamini *et al*., 2019)

48.90%	*Citrus lumia*	Pericarp	Italy	(Raimondo *et al.*, 2018)
58.4%	*Citrus aurantifolia*	Pericarp	Italy	(Spadaro *et al.*, 2012)
57.84%	*Citrus aurantifolia*	Leaves	Nigeria	(Ibrahim *et al.*, 2019)
26.9-54.3%	*Citrus myrtifolia*	Pericarp	Italy	(Plastina *et al.*, 2018)
78.13%	*Citrus junos*	Pericarp	Japan	(Hirota *et al.*, 2010)
91.8%	*Citrus limetta*	Pericarp	India	(Maurya *et al.*, 2018)

Nature and Occurrence of Limonene

Limonene is a cyclic monoterpene with 1-methyl-4(prop-1-en-2-yl) cyclohex-1-ene as its IUPAC name. Its name is derived from its source, lemon, as it was derived from lemon peel first. Limonene occurs as a dipentene, the racemic mixture of R and S enantiomers as shown in Figure 1. Limonene is colorless, sparingly soluble in water and has sweet orange smell(Ciriminna *et al.*, 2014). In the presence of light and oxygen it is prone to autoxidation to yield hydroxyl radicals, ozone and nitrate radicals, like: Cis-limonene-2-hydroperoxide(cis-2-hydroperoxy-p-mentha-6,8 diene),Trans-limonene-2hydroperoxide(trans-2-hydroperoxy-p-mentha-6,8 diene),and L-carvone ((R) – (-)-6, 8-p-mentha-diene-2-one)(Karlberg & Dooms-Goossens, 1997).Since, it is known to be volatile it may undergo gas phase reactions that leads to the formation of aerosol and photochemical smog(Falk Filipsson *et al.*, 1998). When limonene is heated it emits carbon monoxide and carbon dioxide(Naess, 2007). Limonene is flammable, non-toxic but can cause skin irritation upon prolonged exposure to oxidized limonene (Falk Filipsson *et al.*, 1998).



Structure of Limonene A. R-Limonene B. S-Limonene

Fig. 1 : Structure of Limonene

Limonene presence has been revealed in various plants, trees, bushes and citrus fruits. The most common source of dl-limonene is found to be peel of citrus fruits, dill, caraway, fennel, and celery (Akihisa *et al.*, 2003). Good amount of d-limonene is present in orange (>90%), grape fruit (90%), lemon (70%) and celery (60%). The l-limonene is mostly found in pine needle oils, turpentine, spearmint, and peppermint(Smith, 1971).

Commercial applications of limonene

Global production of limonene is estimated to be around 70000 tons per year (Ciriminna *et al.*, 2014). One of the essential economic applications of limonene has been found in the field of food industry in the production of citrus juices. The quantity of the juice consumption depends on the quality and odour of the fruit. The former is enhanced by the limonene. It is also used in carbonated beverages, ice-creams, baked food and confectioneries not only as a fragrant agent but also acts as a potential stabilizer as well (Shaw *et al.*, 1997).

Limonene is also used in cosmetic products such as soaps, shower gels, cleansers as fragrant as well as in aromatherapy(Francis & Bui, 2015; Vieira *et al.*, 2018). It is also an important constituent of various fragrances and perfumes (Ciriminna *et al.*, 2014). In agriculture it is also used as potential ecological insecticide and sometimes as an ingredient of poultry feed (Tammaro *et al.*, 2012). Limonene has also shown the potential of being an eco-friendly alternative to toxic fossil fuel based solvents (Ciriminna *et al.*, 2014). They are also used in the extraction of petroleum from oil sands in different countries (Ciriminna *et al.*, 2014).

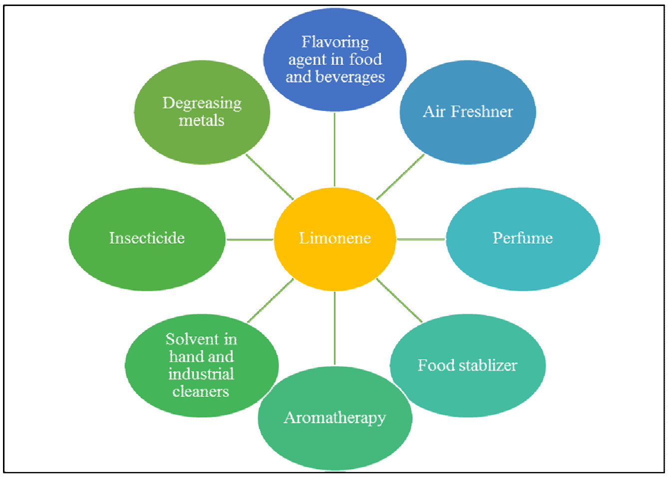


Fig. 2 : Commercial applications of limonene

Therapeutic attributes of limonene

Limonene has not only worked well in the industrial set up but has also paved its way into the healthcare system. Various pharmacological activities of the limonene such as anticancer, anti-diabetic, anti-inflammatory, antidepressant, and neuroprotective activity; and gall stone dissolution ability has been discussed in following sections and also represented in Fig 3.

Antimicrobial activity

Food and juice preservation is becoming more and more demanding because of the food and juice spoilage caused by the certain acid-tolerant bacteria and some yeasts and molds. It is imperative to look for alternative avenues of food preservation. Bevilacqua *et al* has investigated the bioactivity of limonene along with eugenol and reported the anti-microbial action of citrus extract against three bacteria (*Bacillus coagulans, Lactobacillus plantarum, Lactobacillus brevis*) and equal number of yeasts (*Rhodotorula bacarum, Pichia membranifaciens, Saccharomyces bayanus*) which are mainly responsible for the spoilage of fruit juices(Bevilacqua *et al.*, 2010). Limonene has also shown antibacterial effect against different food borne pathogens: *Yersinia enterocolitica, Staphylococcus aureus, Salmonella typhi* and *Listeria monocytogenes* (Han *et al.*, 2020; Lu *et al.*, 2016;

Sonu *et al*., 2018). The destruction of cell wall structure and hindrance of ATP synthesis was reported to be the mechanism behind antibacterial activity of limonene against *L. monocytogenes* (Han *et al*., 2020). Further, it has also shown antibacterial activity against opportunistic pathogens such as *Pseudomonas aeruginosa, Micrococcus luteus*and *Enterococcus faecalis* (Li *et al*., 2019; van Vuuren & Viljoen, 2007). Limonene rich lemon essential oil inhibited the growth of different fish-spiolage bacteria such as *Proteus mirabilis* and *Photobacterium damselae* (Yazgan *et al*., 2019). Limonene isolated from *Citrus bergamia* inhibited the growth of different *Mycoplasma* species (Furneri *et al*., 2012). Apart from antibacterial activity limonene has also shown antifungal activity. Limonene inhibited the growth and biofilm formation of *C. albicans.* Induction of apoptosis was the mechanism behind the antifungal activity of limonene against *C. albicans* (Thakre *et al*., 2018). Similarly, limonene rich citrus essential oils have inhibited the growth of various dermatophytes and other fungi belonging to *Candida, Aspergillus* and *Cryptococcus species* (Flamini *et al*., 2019; Ruiz-Pérez *et al*., 2016).

Antidepressant activity

Depression and its associated symptoms like insomnia, anorexia and lack of concentration is on the rise globally and about 264 million people suffer from depression globally (WHO, 2020). The currently available antidepressant drugs are not effective globally and there are also reports of side-effects of these drugs. So, it is important to look for alternative drug molecules for treating depression. In this regard, limonene can be a potential antidepressant molecule. Limonene inhalation has shown antidepressant activity in mice model with chronic unpredictable mild stress (Zhang *et al*., 2019). Similarly, inhalation of Anshen oil which consists of 24.07% D-limonene has decreased the sleep onset latency time and increased the duration of sleeping time in mice model of insomnia (Zhong *et al*., 2019). R-limonene has also shown antidepressant activity in mice model with spared nerve injury (Piccinelli *et al*., 2015). The mechanism for the antidepressant property of limonene involves the improvement of neuroendocrine, neurotrophic and monaminergic systems (Zhang *et al*., 2019). Other mechanism for antidepressant property of limonene can be the activation of AMP-activated protein kinase (AMPK) pathway. Studies has shown that activation of AMPK pathway has antidepressant activity (Tang *et al*., 2019; Zhu *et al*., 2014). Study by Tang *et al* has shown that the treatment with D-limonene protect neuronal death and show antidepressant activity by activating AMPK pathway(Tang *et al*., 2019). Similarly, inhalation of limonene rich *C. sinensis* showed anti-stress effect sedative effects in mice models (Wolffenbüttel *et al*., 2018).

Neuroprotective Activity

Neurodegenerative diseases are a major public health concern among aging population across the globe. Neurodegenerative diseases cause the gradual damage to the function and structure nervous system. Alzheimer's disease, Huntington disease, Parkinson's disease, dementia and amyotrophic lateral sclerosis are some of the most common neurodegenerative diseases (Berman & Bayati, 2018). Currently there is no treatment for neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. However, limonene has shown neuroprotective property that can be beneficial in the treatment of neurodegenerative diseases. Limonene has shown the ability to prevent the death of cell in the brain and eye imaginal discs of *Drosophila* expressing beta amyloid peptide(Shin *et al*., 2020). Formation of beta amyloid plaques are the major sign of Alzheimer's disease (Shin *et al*., 2020). Antioxidant activity and anti-inflammatory activity of limonene can be the mechanism behind the beneficial effect of limonene in the *Drosophila* model of Alzheimer's disease (Shin *et al*., 2020). Apart from Alzheimer's disease, limonene has also shown potential as anti-epileptic drug. Epilepsy is also a form of neurodegenerative disease which involves loss of neurons and damage to glial cells(Bernasconi, 2016; Farrell *et al*., 2017). About one-third of the epileptic patients are resistant to antiepileptic drugs (Bernasconi, 2016). Hence, it is important to look for novel therapies to treat epilepsy. Limonene based semicarbazones has shown anticonvulsant property (decrease the severity of epileptic fits) in mice models by affecting GABAergic pathway (Rajak *et al*., 2013). Studies have shown that the drugs that decrease GABA synthesis cause epileptic seizures and vice versa(Rajak *et al*., 2013; Treiman, 2001). In mice with models with peripheral nerve injury limonene administration improved the axonal regeneration of sciatic nerve and also enhanced sensory and motor functions(Araújo-Filho *et al*., 2020). These studies show that limonene can be potential neuroprotective agent and help in the treatment of neurodegenerative diseases.

Amelioration of Myocardial Infarction

Myocardial infarction is one of the most prevalent cardiovascular diseases(Younis, 2020). According to World Health Organization's estimate, 32.4 million cases of myocardial infractions and strokes occur annually (Organization, 2013). Studies have shown the potential of d-limonene to protect against myocardial infarctions (Durço *et al*., 2019; Younis, 2020). Durco *et al.* showed that the treatment of murine models with induced myocardial infarction decreased the infarction area and alleviated the damage to the cardiac muscle fibers. Limonene also completely eliminated the oxidative stress based cardiac injury (Durço *et al*., 2019). Similar results were obtained in another study. Younis *et al.* exhibited the reduced infarct area and inflammatory cytokine levels, along with the improvement in blood pressure in the mice models with isoproterenol induced myocardial infarction after treatment with d-limonene(Younis, 2020). Inhibition of the MAPK/NF-κB pathway, reduction of oxidative stress damage and suppression of apoptosis are reported as the mechanism behind amelioration of myocardial infarction by limonene(Durço *et al*., 2019; Younis, 2020).

Gallstone dissolution

Gallstones are formed due to the precipitation of one or more components of bile due to the imbalance in the bile's chemical constituents (Njeze, 2013; Sanders & Kingsnorth, 2007). In developed countries gallstones affect 10-15% of the population(Stinton & Shaffer, 2012). A mixture of limonene and medium chain monoglyceride in 3:2 ratio dissolved more than 99% of cholesterol gallstone and mixed gallstone *in vitro*(Igimi *et al*., 1992). In another study carried out on 200 patients with gall stone to determine the efficacy of d-limonene it was found that in 48% patients the gall stone was completely dissolved and in 14.5% cases the stones were partially dissolved (Igimi *et al*., 1991).

Anti-diabetic activity

Diabetic cases are increasing every day. Currently there are 463 million diabetic patients in the world and the cases are expected to increase up to 700 million by the year 2045 (Saeedi *et al*., 2019). The therapies generally used to control the blood glucose level in diabetic patients include oral hypoglycemic agents, insulin and dietary manipulations. But these have been revealed to have detrimental side-effects such as weigh gain and severe hypoglycemia(More *et al*., 2014). Studies have shown anti-diabetic effect of d-limonene in streptozotocin induced diabetes in murine models(Bacanlı *et al*., 2017; Murali & Saravanan, 2012). Murali *et al* demonstrated that the administration of d-limonene in streptozotocin induced diabetic rats reduced blood glucose level, glycosylated hemoglobin (indicator of diabetes) and increased plasma insulin and carbohydrate metabolizing enzymes. The D-limonene administration to diabetic rats also reduced the activity of enzymes involved in gluconeogenesis (Murali & Saravanan, 2012). In another study, also D-limonene reduced the blood glucose level and increased the plasma insulin levels in streptozotocin induced diabetic rats (Bacanlı *et al*., 2017). Furthermore, D-limonene treatment of diabetic rats decreased the oxidative stress and DNA damage along with the reduction of total cholesterol, low density lipoprotein and triglyceride levels(Bacanlı *et al*., 2017).

Anti-cancer Activity

Several experiments have been carried out for demonstrating the anticancer property of limonene. Limonene has shown anti-leukemic and anti-angiogenic property against chronic myeloid leukemia (CML) (Shah *et al*., 2018). CML causes rapid increase in the counts of white blood cell (WBC), lymphocytes (LY) and neutrophils (NE) whereas reduces the hemoglobin (Hb) content and number of red blood cells (RBC) (Shah *et al*., 2018). Treatment of murine models of CML with d-limonenedecreased the counts WBC, LY and NE and increased the Hb content and RBC counts. Furthermore, D-limonene also inhibited angiogenesis, formation of blood vessels which is necessary for the growth, dissemination and metastasis of tumors (Shah *et al*., 2018). Limonene has also shown anticancer activity against hepatocellular carcinoma by inducing apoptosis of cancer cells (Hafidh *et al*., 2018). Intake of 2 grams of limonene every day by women with breast cancer reduced the expression of cyclin D1, a biomarker of breast cancer (Miller *et al*., 2013). Cyclin D1 plays an important role in the cell cycle progression and is overexpressed in intraductal carcinoma of the breast (Miller *et al*., 2013). The co-treatment of limonene and linalyl acetate reduced the viability of human neuroblastoma cells *in vitro* by activating apoptosis(R. Russo *et al*., 2013). D-limonene rich orange volatile oil inhibited the angiogenesis, metastasis and proliferation of human colon cancer cells (Murthy *et al*., 2012). The limonene along with its hydroxylated derivative have shown good anti-cancer activity when cancer was induced by DMBA I, e dimethylbenzathracence. The rat models under investigation were given 5% limonene before1 week prior to induction cancer with DMBA carcinogen. The tumor cells showed a significant decrease and the number was found to be half the value of control (Crowell *et al*., 1992). Limonene also inhibited the proliferation of human adenocarcinoma and hepatocarcinoma cell lines in vitro (Manassero *et al*., 2013). D-limonene inhibited the pulmonary adenoma formation in mice with carcinogen induced neoplasia of the lungs (Wattenberg & Coccia, 1991). These studies show the potential of limonene and limonene rich citrus essential oils as anticancer agent that can inhibit angiogenesis, growth, proliferation, and metastasis of tumor cells.

Anti-inflammatory Activity

Limonene acts as a potential anti-inflammatory agent as well. Administration of limonene decreased edema and showed anti-inflammatory effect in rats with carrageenan induced edema(Yilmaz & Özbek, 2018). The inhalation of limonene by the asthmatic rats reduced the bronchial constriction and the peribronchial and perivascular inflammatory cell infiltration (Keinan *et al*., 2005). The anti-inflammatory response has also been confirmed, via, the inhibition of 5-lipoxygenase by limonene obtained from *Helichrysum odoratissimum* (Frum & Viljoen, 2006). 5-lipoxygenases are necessary for the synthesis of luekotrienes which are responsible for the mediation of inflammation (Radmark & Samuelsson, 2009). The mechanism behind the anti-inflammatory property of limonene could be the activation of A_{2A} adenosine receptor(Patel *et al*., 2020). A_{2A} adenosine receptor is a G protein coupled receptor that mediates bronchodilation and could prevent bronchoconstriction and inflammation in asthma (Patel *et al*., 2020). The inhibition of pro-inflammatory mediators such as tumor necrosis factor-α can also be another mechanism behind limonene's anti-inflammatory activity (Kummer *et al*., 2013). Other mechanisms can be the inhibition of cytokine, eosinophil migration and reactive oxygen species (ROS) production (Hirota *et al*., 2010). ROS mediated oxidative stress is responsible for the atherosclerosis and other inflammatory diseases (Bus & Gibson, 1982; Kaur *et al*., 2017; Young & Woodside, 2001).

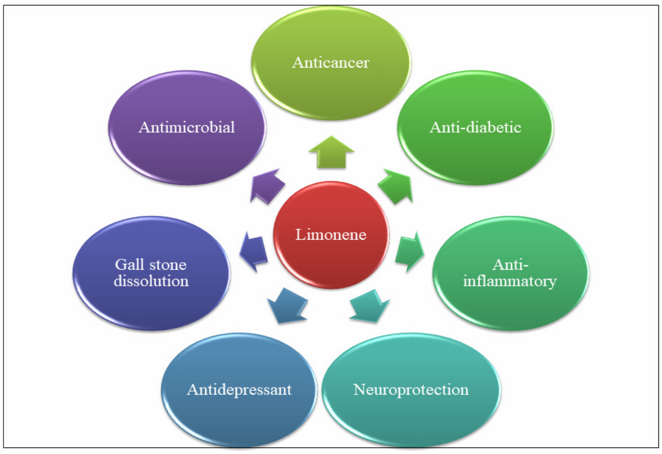


Fig. 3 : Therapeutic activities of Limonene

Extraction methods of limonene

Essential oils in general and limonene in particular have a wide variety of applications in the manufacture of consumer goods like soaps, cosmetics, perfumes, pharmaceuticals, soft drinks etc. The demand of these products is increasing day by day and so is the production demand of essential oils (Ümit Ünal *et al*., 2012). The two conventional and common methods used for the extraction of essentials oils are discussed in brief below:

Conventional Methods

Hydro-distillation with Clevenger set-up

Hydro-distillation with Clevenger set up is one of the traditional and easiest methods used for the extraction of essential oils from plants as well as fruits. The plant or fruit from which oil is to be extracted is put into the round bottom flask and controlled heat is applied(Leitzmann, 2016). On applying heat the oil gets freed from the oil glands. Once the oil is freed it gets evaporated along with the solvent. The oil and the solvent gets liquefied in the condenser because of the flow of cold water through inlet and outlet pipes. This is followed by the collection of the oil in the decanter along with the solvent. Since, oil is less dense and least soluble in water it forms a separate layer on top of the solvent. Using the micro-pipette the oil is carefully separated from the rest of the solvent. The set up consists of the round bottom flask, condenser, heating mantle, thermometer, inlet and outlet flow (Ismaiel *et al*., 2016; K. A. Shah *et al*., 2017). This method has been used for the extraction of essential oils from *C. sinensis* peels (Liu *et al*., 2019).

Steam-distillation process

It is an old distillation process which is used to extract essential oils that are temperature sensitive (aromatic compounds).This method is rarely used now because has been replaced by more sophisticated and more accurate apparatus called vacuity distillation and microwave steam distillation (Mahato *et al*., 2019). The plant material is kept in distillation apparatus and is subjected to steam. The volatile oil molecules get released from the oil gland and start evaporating. Then, the steam containing the volatile oil gets through the cooling system where it changes into the liquid form due to the condensation process. Further separation of the oil from solvent is done exactly the similar way as it is done in the case of hydro-distillation process. The process though not so common now has wide range of applications as because of higher amount of the oil yield, reproducible oil yield control over the essential parameters like steam and temperature so as to prevent the damage to oil components (Masango, 2005; Shaghaleh *et al*., 2018). This method has been used for the extraction of *C. auranticum* essential oil(Kusuma *et al*., 2016).

Cold press method

Cold press method is a traditional, mechanical and eco-friendly method of essential oil extraction (Çakaloğlu *et al*., 2018). The peels are lacerated with needles to release oils from epidermis and oil glands. The oil is then collected in decantation vessel by water. The water emulsion is then centrifuged to separate the essential oil from the water. The essential oil is dried using anhydrous sodium sulfate and can be stored at 4^0C for further use (Ferhat *et al*., 2007). This method has been used for the extraction of essential oil from *C. medica* and *C. limon* (Ferhat *et al*., 2007; Menichini *et al*., 2011).

Novel Methods for Limonene Extraction

The most common disadvantage associated with the conventional methods for extracting the essential oils is that numerous essential oils are thermo labile in nature. The higher temperature may often lead to changes in their chemical composition with the processes like hydrolysis, oxidation and isomerization. This results in the decrease of quality essential oils. With the advancements in the field of technology, novel methods have been developed and designed for maintaining the quality of the EO's. However, these techniques are often costly but are still used for extracting the valuable and important EO's so as to maintain the structure and integrity of its components. Besides conventional methods are also time consuming and require abundant amount of solvent (Elyemni *et al*., 2019). Some of those novel methods are below described in brief:

Micro-wave assisted hydro distillation (MAHD)

MAHD is an advanced technique of conventional hydro distillation process. In this technique the heating mantle is replaced by the microwave oven. It is a quick and selective method and requires very less amount of solvent. This method is used to extract the essential oils from the solvent on the basis of dielectric constant (Bousbia *et al*., 2009). Depending upon the polarity of the solvent and the extract the conduction and dipole rotation occur simultaneously and thus reach to two different levels in the condenser couple and are finally separated from each other (Rezaei, 2008). This method is efficient but very costly. This method has been used for the extraction of limonene rich essential oils from *C. limon, C. reticulata and C. sinensis*(Shakir & Salih, 2015).This method has shown to be efficient and rapid method for the recovery of D-limonene from citrus peel as compared to conventional heating method(Attard *et al*., 2014). Furthermore, this method also improved the yield, recovery and quality of the d-limonene from citrus peels (Attard *et al*., 2014; Putnik *et al*., 2017).

Solvent free micro-wave extraction

The method is used to carry out extraction of essential oils without using any solvent or water (Lucchesi *et al*., 2004). Initially the plant from which oil is to be extracted is soaked in water for about 1-2 hours. This is followed by draining off excess water and then exposing to the controlled heat of microwave. The parameters like temperature and extraction time is controlled by using a panel of the instrument. The microwave heats the *in situ* water in the plant materials expand the plant cells leading to the rupturing of oil glands and oleiferous receptacles (Lucchesi *et al*., 2004; Uysal *et al*., 2011). Then, the essential oil rich in limonene is freed and evaporated which in turn is condensed by cooling system present outside the microwave (Lucchesi *et al*., 2004). The essential oil is collected and dried using anhydrous sodium sulfate. Then,it can be stored at 0°C until further usage. This method has been used for the extraction of *C. paradisi* essential oil (Lucchesi *et al*., 2004; Uysal *et al*., 2011).

Ultrasound Assisted Extraction

This method combines ultrasound wave and conventional hydro-distillation method of essential oil extraction. Instead of heating mantle or microwave, ultrasound waves is used. During ultrasonication the collapse of air bubbles rupture the oil glands and cause the release of the essential oils from which limonene can be isolated by using conventional hydro-distillation method (Putnik *et al*., 2017). An increase of 44% yield in essential oils from Japanese citrus was reported when ultrasound assisted extraction method was used in comparison to the traditional methods (Mason *et al*., 2011; Putnik *et al*., 2017).

Superficial Carbon dioxide Fluid Extraction

This method is used to extract and separate components using supercritical fluids like carbon dioxide (CO_2) as solvents(Wang *et al*., 2016). Supercritical CO_2 has the property of both gas and liquid. Due to the property like gas in can reach to small places and due to the property of liquid it can act as a solvent. As the properties of the supercritical CO_2 can be easily manipulated, it can bind with any substance and help in its separation (Sapkale *et al*., 2010). Plant materials are ground and kept inside the extraction vessel. The, CO_2 at high pressure and temperature is forced by a pump into the extraction vessel where supercritical CO_2 dissolves the plant material. The, by changing the pressure, temperature and flow rate, the CO_2 can be manipulated to bind with molecule of choice and get it separated. This method has been used to obtain essential oil from *C. medica* and *C. latifolia* (Atti-Santos *et al*., 2005; Menichini *et al*., 2011).

Toxicity associated with limonene and its epoxides

Limonene has very low toxicity but it can be irritating to the eyes and skin (Falk Filipsson *et al*., 1998). For rats the lowest LD50 (Oral) is found to 4600mg/kg (Karr, 1989a). However the limonene of citrus origin has been found to be slightly toxic towards insects (Pereira *et al*., 2010). When limonene is being used in pure form it showed toxicity towards insects like cowpea weevil, rice weevil and termites (Karr, 1989b; Pereira *et al*., 2010). However, the application of *C. limetta* essential oil which mostly consists of limonene (91.8%) did not cause toxicity in vitro and in vivo studies and showed safety for topical application on skin (Maurya *et al*., 2018). Similarly, *C. sinensis* essential oil which contain 96% limonene did not cause cytotoxicity to human oral epithelial cells and also did not cause any genotoxicity while performing Ames toxicity assay (Ruiz-Pérez *et al*., 2016). Although studies conducted so far affirm that limonene and limonene rich essential oils do not cause serious toxicity, their epoxides can be harmful. When limonene epoxide was administered intraperitoneally in the lower doses of 25, 50 and 75 mg/kg it did not show any toxicity for 14 days in animals under study (de Almeida *et al*., 2012). Upto 1000mg/kg concentration no mortality was reported. But when the dose was increased to 2000mg/kg body weight, death of mice was reported within 72-120 hours and at the dose of 4000mg/kg body weight the death occurred 2-36 hours (de Almeida *et al*., 2012). These studies show that limonene and it epoxides are not toxic but at very high dose they can have lethal consequences. Compounds with LD50 between 500-5000 mg/kg are considered to be slightly toxic (de Almeida *et al*., 2012).

Conclusion

The present world researchers are dedicated to improve the quality of human living as well maintaining environment in its purest form. The two key areas which will contribute slightly in achieving the goals include: waste management and treating various diseases. Regarding the waste management the non-edible parts of fruits that come from the homes and fruit industries also add to the heaps of wastes. Extraction of limonene from citrus peels can help to manage the pollution caused by citrus wastes. Limonene is of utmost importance with regard to its applications in different industrial set-ups too. Though, it is abundantly found in different natural sources, yet its vast studies remains obscure. This review has given an extensive outlook of the various extraction methods which includes both conventional as well as novel methods. This review discusses the numerous potential therapeutic properties of the limonene such as anticancer, antimicrobial, anti-inflammatory, anti-diabetic and antidepressant. The mechanism behind these properties has also been discussed. The possible toxicity of limonene has also been reviewed.

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