

Thujone in Daily Life – A Review on Natural Sources of Thujone, its Side Effects and Reduction Mechanism of Thujone Toxicity

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ABSTRACT

Thujone is a natural or manmade ketone monoterpene, fragment substance which is most famous for its use in absinthe spirit. It is found in various plants which are used as medicines, foods, hard drinks, and for various purposes in our daily life. The plants that contain thujone are wormwood, clary, tansy, sage, some junipers, oregano, thuja, cypress, mentha, lavender, etc. So it is likely to use thujone-containing plants for food and medicine can be harmful to our body. It has been reported that long-term use of these plants may lead to diseases like stomach aches, seizures, renal failure, hallucination, rhabdomyolysis, paralysis and even death. In current review we have discussed different toxic effects of thujone and have tried to search the plausible solutions by which we can minimize or remove the thujone from daily used plant products.

Key words: Thujone, Plants, Foods, Medicine, Toxicity, Reduction

INTRODUCTION

Thujone is a monoterpene ketone which is found in wide variety of plants. The presence of thujone in any sample can be detected and quantified by Gas Chromatography-Mass Spectroscopy (GC-MS) (1). The ratio of α -thujone and β -thujone is vary from plant to plant. It has been reported that it can be used as insecticide (2). In rat model α -thujone can be used as treatment in Polycystic Ovary Syndrome (POS). α - thujone can increase estradiol, progesterone and decreased significantly luteinizing hormone (LH), testosterone level (3). Beside its beneficial role, thujone is considered as toxic compound, and mostly neurotoxic (4). Thujone has two isomers α -thujone and β - thujone. Percentages of α -thujone and β - thujone vary in different plants. α -thujone is comparatively more toxic to its β -isomer (5). Consumption of thujone containing plants may cause seizures (6). α -thujone was found to inhibit GABA_A receptor. In an experiment, the 3 days old chick got fear and anxiety after the treatment of high dose of thujone (7). Both α - and β - thujones act as non-competitive blocker and it blocks chloride channel in GABAergic neurotransmitter. α -thujone is porphyrogenic and it can affect hepatic damage (8). Due to its neurotoxicity it is used as insecticide. In present study we have discussed the chemical composition of thujone and its natural sources. Thujone is found in several plants

which have huge medical value but the amount of thujone varies in different plants and its products. But long term uses of low thujone containing plants and short term used of high thujone contains plant can be harmful for our body. To overcome this problem we have to produce thujone free food and medicine or with trace amount of thujone which can not affect our health.

Chemical Property

Thujone, C₁₀H₁₀O colourless terpene like ketone, which is commonly known as 3-thujone. Its chemical structure similar with camphor. The smell of thujone is methanol-like. It is collected from natural resources (plants) and even manmade (9). The thujone has two forms levorotatory (-) α -thujone and dextrorotatory (+) β -thujone. α -thujone is present in greater amount than β -thujone.

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For quantification of thujone isomers GC-FID (Gas Chromatography with Flame-Ionization Detection) calibration curve method is used (10). In absinthe-thujone is an "active" ingredient. The thujone concentration does not change at 100% ethanol and 30% ethanol in a pH range between 2.5-6.5. But at 11.5pH an epimerization between α -thujone, and β -thujone occurs rapidly and the ratio reach 1:2 (α -thujone: β -thujone) (11). α -thujone is more toxic than β -thujone. The chemical composition also changes with different season (12,13).

Table 1. Computed property of thujone

Property name	Property value
Molecular weight	153.23
Hydrogen bond donor count	0T
Hydrogen bond acceptor count	1
Rotatable bond count	1
Heavy atom count	11
Complexity	207
Formal charge	0
Covalently-bonded unit count	1
Compound is canonicalized	Yes
HDB	0

Structure

The stereoisomers of α - and β - thujone present in the sage plant which was detected by headspace solid-phase microextraction - gas chromatography-mass spectrometry. But the stereoisomers are not commercially available. To identify α,β -thujone in thujone containing essential oil chiral resolution is used (14). The other names of thujone are Bicyclo [3.1.0] hexane -3-one,4-methyl-1-(1-methylethyl); 3-Thujone; (-)-Thujone; NSC 93743etc. IUPAC (International Union for Pure and Applied Chemistry) name of thujone is 4-Methyle -1-(propan-2-yl)bicyclo[3.1.0]hexane-3-one (15). Synonyms of α -thujone are (+)-Isothujone, (-)-3 Isothujone, (-)-3-thujanone,

Absinthol, dl-Thujone (16). Synonyms of β -thujone are (+)-Isothujone, (+)-3-Thujone, Isothujone, d-thujone, D-beta-thujone, trans thujone, D-beta,(+)-b-thujone (Figure 1) (17).

Solubility

In water: 0.6 mg thujone can be extracted by dissolving 1 mg thuja in water. As its alcoholic behavior it can not soluble in water (18). It was found that thujone is less solvable in water. Thujone can kill germs (19). Only 8% of thujone is recovered in water. Thujone containing Artemisia is more active, less toxic, and less stable in water but in oil or lipid, it is more toxic, more stable, and can cross the blood-brain barrier (BBB) (20).

In Alcohol: Thujone is more soluble in alcoholic content than water. Thujone in alcohol content is more toxic than alcohol alone for our body (21). Absinthe flavoured spirit was very popular in the late 18th century in Switzerland and in 19th to 20th centuries it was popular among Parisian artists and writers. It is derived from plants' leaves and flowers and it is rich in thujone (22). As it is soluble in alcohol, the liquid-liquid extraction method is used to identify the compound thujone in herbal, food drinks, soft drinks, or alcoholic beers (23,24).

Stability

Thujone is stored in green glass bottle which minimize the loss (up to 20%). The colouring happens after high UV exposure in clear glass bottles. The thujone from natural resources is highly stable in absinthe and it is also stable in 100% ethanol and 30% ethanol at pH 2.5 or 6.5. But at 11.5 pH α -thujone converts to β -thujone (25,26). The conversion happened at 20^oc in sunlight or darkness and it takes 20h to get an equilibrium state of about (1:2) (alpha thujone: beta thujone). If the temperature varies upto 100^oc the reaction rate does not vary (11). The stability of absinthe where thujone is presently increased by at 50^oc for 5-25h. This, in suitable temperatures and dark conditions, it can be used for at least 1 year. Stability of thujone is measured by GC, GC-MS, and GC-FTIR (Gas

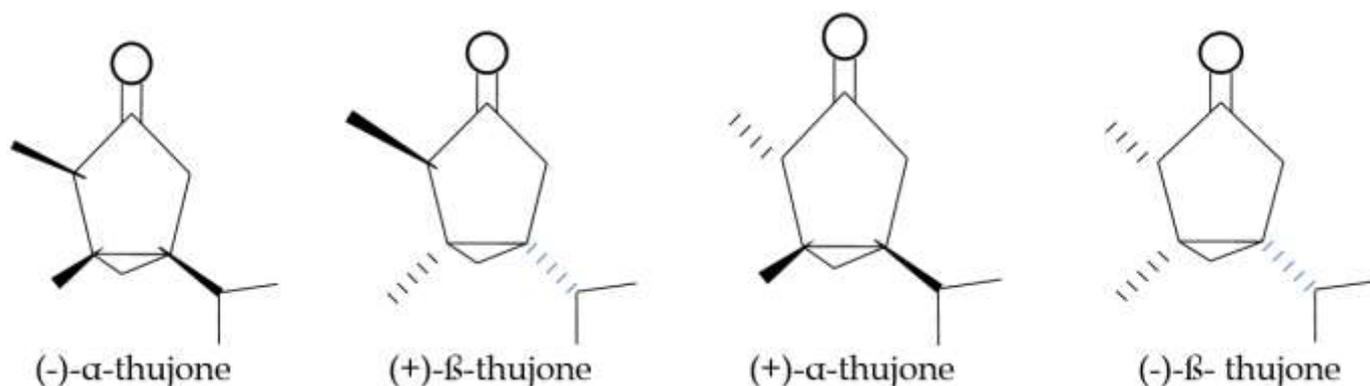


Figure 1. Isomers of α - and β - thujone and their structures

Chromatography Fourier Transform Infrared spectrometer) (27). The stability of α and β thujone in wormwood flavored spirit or bitter liqueur is decreased by keeping it in oak barrels or kept in stainless steel barrels or commercial glass bottles (28). Thujone reduction in phosphoric acid or potassium nitrate is quassireversible and adsorption is controlled by a two-electron process. They are voltammetric experiments by adding ethanol and Triton X-100 (29). During plant development, α thujone is decreased significantly but in flower oils, both isomers of thujone are stable and α thujone is found in greater amount than β thujone and their accumulative amount is also increased (30). The thujone is stable in normal ambient and in anticipated storage with suitable temperature and pressure (31).

Plants Sources

Thujone is an essential oils component that is derived from wormwood, mugwort, sage, clary, tansy, and thuja. Many thujone-containing plants are used for intestinal worm treatment for its anthelmintic effects and are also used in wine, tonics carminatives, and astringents (Table 2)(1). The thujone is found in greater amount in some plant families (e.g. Asteraceae or Cupressaceae). Many flowering thujone containing plants are used in food making (32). Thujone is found in Nootka cypress, some junipers, oregano and menthe (33). In the lavender constitutes maximum amount of thujone (34).

Table 2. Different thujone containing plants and their use in daily life.

SL No.	Plant Name	Parts of Plant used in daily life
01.	Wormwood	Stems, leaves, roots
02.	Mugwort	Stems and roots
03.	Sage	Leaves
04.	Clary	Leaves, flowers, stems, and seeds
05.	Tansy	Stems
06.	Thuja	Leaves
07.	Cypress	Leaves, cones, wood, branches
08.	Oregano	Leaves, stems, flower buds
09.	Juniper	Berry, branches, leaves
10.	Menthe	Leaves, flowers, stems, bark, seeds
11.	Lavender	Buds, Stems, leaves

Daily use of Thujone Containing Plant

Wormwood

The thujone is a major substance in the wormwood plant but the plant is commonly used in food, drink, and herbal medicine nowadays. The plant is used in the preparation

of tea which helps in stimulating digestion and improves appetite. This plant popular for its used in the treatment of several diseases like crown's disease, stroke, and Alzheimer's disease (35). It can be used in a parasite-mediated intestinal disease. The wormwood oil is used in healthy food in the U.S. and is also used for the treatment of gallbladder disbalance. Because of the presence of thujone in wormwood oil doctor's advice avoiding the wormwood oil (35). 100 types of absinthe are now available legally. In myths, legends, and lay literature in European countries wormwood oil is used in the preparation of absinthe. In various German and French recipes, wormwood is used. It is also used to make high-quality flavoured spirits (36). It is used as an antibiotic and also used as medicine for several diseases like hepatitis, gastritis, jaundice, anemia, anorexia, indigestion problem, and dysplasia. It also has antioxidant, antifungal, anticancerous, analgesic, immunomodulatory, cytotoxic activity and antimalarial activity (37).

Mugwort

The plant is found in mountains of various countries. Used as medicine as antispasmodic, anthelmintic, and in stomach disruption. It is used also as insecticide and larvicide. In Chinese medicine, its leaves are popularly known as 'Ai Hao' which is used as medicine for diarrhea and hematoma disease (38). Thujone is a mutagenic component but in mugwort, some nonmutagenic components like AFB1 (Aflatoxin B1) can reduce thujone mutagenicity but mechanism of action not clear. It is also used as medicine in Korea and oriental countries. It is also used in perfumery and tea. It has antibacterial effect and used to remove pathogen (39).

Sage

Sage which belongs to family Labiatae has a wide range of pharmaceutical activities (40). It contains vitamins like A, C, E, and K; magnesium; zinc; copper in little amounts, and it provides calories, protein, fiber, and carbs (41). Sage is used as flavour in food industry. It is used in photochemistry and has therapeutic application. It constitutes 160 different types of polyphenol (42). Sage also has chlorogenic acid, rutin, caffeic acid, rosmarinic acid, and ellagic acid which can improve health and fitness, lower the risk of cancer, and improve memory (41). It has antibacterial activity and used as a mouth wash for dental cavity wash (43). In menopause hot flashes, excessive swelling, irritability, and vaginal dryness symptoms can be reduced by the treatment of sage herbal medicine (44). Sage can reduce blood glucose levels by activating a specific receptor (PPAR γ) which can reduce free fatty acids (45). It is used as medicine for Alzheimer's disease and it can reduce bad LDL cholesterol. It can fight against mouth, colon, liver, cervix, breast, skin, and kidney cancer. It is used in various dishes for its aromatic flavor for the better test (41).

Clary

Clary sage oil has importance in aromatherapy during the menstrual cycle, childbirth, and menopause. Nowadays it is used as an anti-stress, anti-depression, analgesic agent, cytotoxic, anti-oxidant, and anti-microbial agent (46). Clary sage total plant juice is used as mucous cleaning in eye disease and its aqua extract is recommended as digestive, carminative, and aperitif. It is also used as a mouth wash (47). Clary is used in food and perfumery products. It is used as an essential oil, personal health care products, and anti-cancer and its flavour is like tobacco (48).

Tansy

It is an everlasting plant that is found in the northern hemisphere. It is used in many food recipes like salads, omelets, cakes, and in various foods as spice. It acts as an anthelmintic medicine, improve for loss of appetite, and migraine and also acts as an antimicrobial agent. It is also used as a pesticide (49). Tansy is used as an essential oil. It is used in perfume making for its aroma nature (50). Tansy essential oil has antioxidant activity. It is used as food preservative and as a pharmaceutical agent. It is an active component of antifungal, anthelmintic, diuretic medicines (51).

Thuja

The thuja plant is found mainly in European countries. It is used as traditional homeopathic medicine for the treatment of tumours, vital organs. The homeopathic mother tincture (TOφ) and Thojone Rich Fraction (TRF) are separated from thujone leave extract and used against cancer (52). Thuja has an antiatherosclerotic property by which it can increase HDL in the whole cholesterol ratio and reduce the atherogenic index in EFTO (Ethanol Fraction of extract of aerial part of Thuja Occidental) treated groups (53). It has antiviral activity and it also has immunopharmacological potential for a stimulatory and co-stimulatory effect on antibody production and cytokine production. Thuja polysaccharides (TPS) fight against Human Immunodeficiency Virus-1(HIV-1) dependent cell death and are nontoxic for MT-4 cells in 625 µg/ml concentration (54). *T. occidentalis* have phytotoxic property by which it can prevent seeds from germination of *A. caudatus* and *L. sativum*. The essential oil of thuja has antifungal activity (55).

Cypress

Cypress tree is found in North America, Asia, and the eastern Mediterranean region in huge amount. It is used in the treatment of haemorrhoids and hyperhidrosis. Extract of different portion of plant is used as antiseptic, antioxidant, anticancer, antidiabetic, neurobiological, anticoagulant, hepatoprotective, antibiotic, wound healing, and antiosteoporotic property (56). The saponins and phenolic extract of cones and seeds of cypress are

used as antidiabetic agents (57). Essential oil of cypress leaf has anticancer and antiproliferative properties. It can inhibit human amelanotic melanoma cells and it has *in vivo* and *in vitro* anticancer activity (58).

Oregano

Essential oil of oregano has antibacterial activity against *Streptococcus pyogenes* and it also has anti-biofilm activity (59). It is used as an insecticide and is eco-friendly (60). The essential oil of oregano can decrease the triglycerides level of blood and increase the body weight (61). Oregano essential oil has antifungal and antioxidant activity (62).

Juniper

Juniper essential oil which is an extract from juniper barriers has antibacterial, antifungal effect. Its activity against gram-positive and gram-negative bacteria is the same (63). The Juniper berry essential oil influences the growth. It can increase the protein level; decrease serum cholesterol, triglyceride, glutamic pyruvic transaminase, and alkaline phosphate level (64). Juniper berries or their plant extract is used as diuretic, antidiabetes, antiseptic, and anti-arthritis. It is also used in gastrointestinal and autoimmune disorders. The berries have cytotoxic, hypoglycemic, hypolipidemic, and anti-inflammatory effects (65). The berries reduce the serum levels of aspartate and alanine aminotransferase, bilirubin, and alkaline phosphatase, hence curve hepatic damage (66).

Menthe

It is a species that is used as medicine for long time. It is used as an antiseptic and can improve digestion. The medicine prepared from leaves and flowering stems are used as antispasmodic, choleric, CNS stimulant, and carminative. The essential oil of mentha is used as an antibiotic (67). Its essential oil of it has antifungal and anti-aflatoxigenic efficiency. It is used as an insecticide for food protection (68). The medicines obtained from menthe plants have antioxidant, anti-inflammatory, anti-carcinogenic, antiviral, anti-allergic, anti-tumorigenic and anti-microbial effect (69). Menthe can reduce blood cholesterol, glycemia, LDL-c, VLDL-c Triglycerides, and glucose level. The crude extract of the plant has an anti-diarrheal anti-antispasmodic effect by calcium channel blockage (70).

Side effects of thujone on health:*Seizures*

In an experiment 25mg/kg dose of thujone can cause seizures in mice. Some female mice showed seizures even at 3 and 6 mg/kg doses of thujone. α and β thujone have a serious impact on GABA_A receptors when one consumed for the long time (71). Seizures occur in the male rat at an dose of (11mg/kg BW/day) for long-term use. It can cause

mortality due to long term use and use in low doses (72). The essential plant-derived oil which contains thujone can affect a well healthy person and cause chronic seizures and epilepsy (73). Long term use of absinthe of wormwood can cause epileptic. Thujone-associated seizures can leads to epilepsy (74). In a case study a seven month child was treated with homeopathic medicine which contains thujone caused eight generalized tonic-clonic seizures but When the medicine was not given to the child and was treated with phenobarbital cure seizures (75).

Renal failure

Thujone at 25 mg/kg has an observable effect on kidney function (in hepatic and renal). At 5mg/kg blood urea level is significantly increased (76). If one intakes an overdose of thuja plant extract it has an irritant effect on the kidney or renal system. It happened because of the presence of thujone in this plant extract (77). *A.afra* plant has a high dose of thujone content and anyone intake plant containing thujone regularly and large quantity renal damage may cause vomiting, restlessness symptoms may occur (78). From a case report essential oil and plant extract of wormwood cause acute renal failure and kidney damage due to its high thujone content (79).

Rhabdomyolysis

There are many cases of unusual cramps in muscles due to various doses of thujone. One 54-year-old woman intake an excess amount of sage oil and she was found

with mussel cramp in her tongue and she could not move her tongue. In another case a 53 years old man take essential; oil from sage for many months and he got muscle ache and the muscle enzymes increased rapidly. In another study, a 12 months old girl applied eucalyptus, pine, and thyme oil during bath for 4 days. Her arms, legs and tongue are fixed (80). Thujone reduces choline and induced Ca^{+} from vertical concentration. It can also induce the function of the $\alpha 7$ -nACh receptor (nicotinic acetylcholine) which is important for neurotransmitter release, second messenger cascades, cell survival, and apoptosis (81). 100 μM thujone can inhibit 80% of Acetylcholine (ACh) in human $\alpha 7$ -nAChRs and inhibits 30% of $\alpha 4\beta 2$ -nAChRs. But there is no effect on $\alpha 3\beta 4$, $\alpha 3\beta 2$ and $\alpha 4\beta 4$ -nAChRs (82). The essential oil of sage containing thujone affect cardiac muscle in high dose of it (83).

Hallucinogenic

If a person takes absinthe got affected by various symptoms like excitation, convulsion, and even hallucinations (84). In the 19th and 20th centuries, an 'absinthism' disease was happened for consuming absinthe in high quantity. If a person is addicted to absinthe and takes it for prolonged period he may suffer with blindness, hallucination and mental deterioration (85). The thujone and Δ^9 -THC (Δ^9 -tetrahydrocannabinol) are similar in structure and the active component of marijuana. For their similar structure, they work in a same way and bind to some brain receptor (86). Auditory hallucination also occurs due to consumption of absinthe (87).

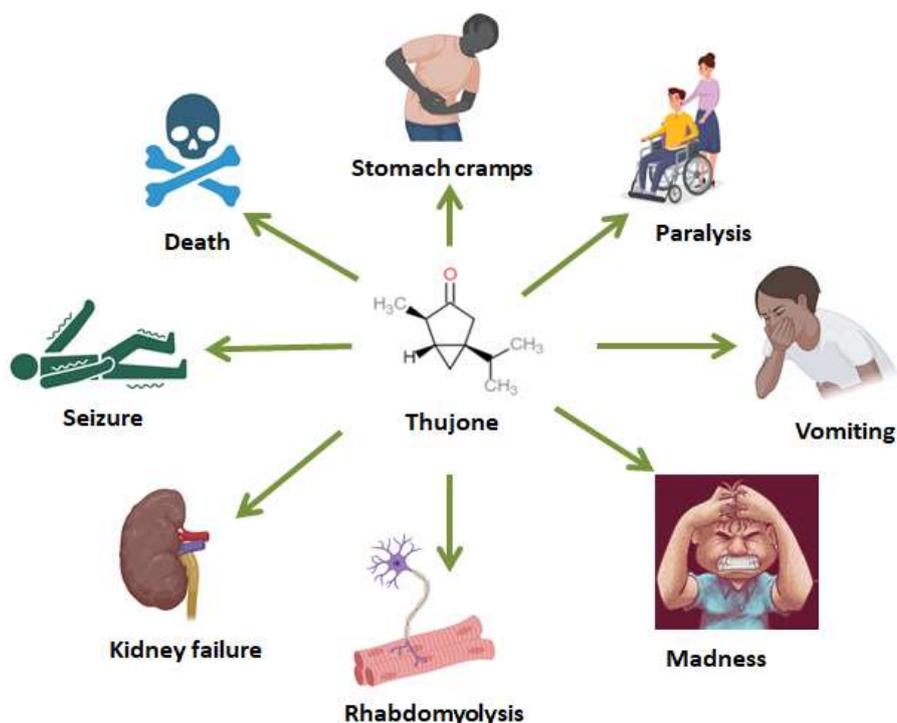


Figure 2. Different side effects of thujone.

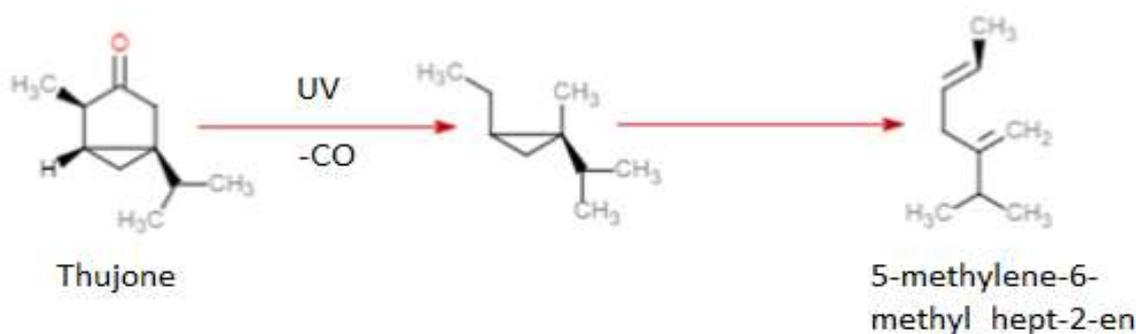


Figure 3. UV irradiation decreased the concentration of Thujone.

Paralysis

β -thujone can affect the helminths central nervous system leads to paralysis and even death (88). The absinthe which contains thujone has an alcoholic property (89,90). Essential oil that contain thujone compound are lethal to the insect as they damage the nervous system which causes paralyze to the insect (91).

Stomach Aches

Essential oils which contain thujone causes vomiting, diarrhea, and stomach aches-like symptoms in humans (92). For stomach aches thujone containing herbal plants is used but their excessive use may cause vomiting, stomach and intestinal cramps symptoms (93) β -iso thujone is responsible for these symptoms in human (94). 3-5 mg/day/person dose of thujone is safe for humans but the overdose may cause high blood pressure, blood glucose, and stomach cramps in humans (95). The thujone containing plant's stems, fruits, and mature leaves ingestion causes severe stomach cramping, nausea, persistent diarrhea, and emesis (96).

Death

60mg/kg thujone showed 100% mortality. Mice with a higher dose of thujone showed toxic effects at 30-45 mg/kg and the mice become paralyzed and even found dead. From this medical treatment, mice can recover before death. Thujone is found in many plants and the α -thujone affected the human body by causing convulsions and causing death (97). A high dose (45mg/kg) may lead the mice to death in 1 minute (98). The essential oil of *Oleum tenacity* which contains thujone can cause death (99).

Reduction of thujone toxicity

Nanoencapsulation

If thujone containing plant wormwood essential oil given with nanoencapsulation to mice (30mg/kg) 4 times per day and continue the process for four days do not have any sign of weight loss and death mice (93).

Nanoencapsulation is a drug delivery therapy that is used in modern day. It is used to prevent much life threatened diseases and it can deliver the drug more efficiently than other lipid-based drug delivery systems (100,101)

Filtration

β -thujone has 100% fumigant toxicity in the adult male when treated with 20 mg/ filter paper. On the other hand, toxicity reduce to 17.5% at 10 mg/ filter paper (102).

Charcoal treatment

In an experiment goats were treated with a high amount of juniper berries which contain thujone-like terpenoid. But their serum charcoal level can reduce thujone toxic effects and they can consume a huge amount of juniper berries in their later life. The presence of charcoal reduces soft tissue damage and liver damage which are caused by thujone in it (103, 104).

Oak barrels

If the thujone containing sample, bitter liqueur 'Pelinkovac' is stored in the oak barrels rather than in stainless steel or glass bottles, the amount of thujone is more in amount after one year (28).

UV irradiation

Under UV irradiation the total amount of α and β - thujone concentrations are decreased in different media sequentially like hexane>30% ethanol>pH2.5>100% ethanol>pH 11.5 (Figure 3) (26).

CONCLUSION

In Current review we have tried to give emphasizing on harmful effects of thujone on our health. Thujone is a terpene-like chemical present in many food products, medicine, alcohol, in many health care products, and insecticides. Those products are prepared from many plants like wormwood, mugwort, sage, clary, tansy, thuja, cypress, oregano, juniper, menthe etc. From those plants, many plants are famous in worldwide use. If we do not

concern about thujone toxicity and we randomly intake those medicine, foods, and alcohol can cause seizures, renal damage, rhabdomyolysis, hallucination, paralysis, and stomach ache-like disease and even death also. We can avoid thujone toxicity by remove of thujone from medicine and foods which are consumed daily. We need to further research on the safe manufacture of medicine and food. For this, all people can consume those product without any fear. In some insecticide thujone is used as natural insecticide which may contaminate the vegetables and harm the consumers. So we also need to find the possible alternatives of thujone in paste management.

Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

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