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Estragole: A review of its pharmacology, effect on animal health and performance, toxicology, and market regulatory issues

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Abstract

Estragole is a volatile terpenoid molecule found in various plants or components, frequently in very high concentrations. It has been demonstrated to increase animal health and output performance effectively. Estragole has been shown to possess antioxidant properties both in vitro and in vivo. These properties include the ability to raise GSH and GPx levels, as well as the ability to suppress toxic materials and maintain cellular redox status, MDA activity, and MPO activity. In addition, it produces anti-inflammatory and immunomodulatory effects via the production/release of cytokines, substance P, bradykinin, histamine, serotonin, cytokines, and nitric oxide (NO), and it induces a substantial leukocyte migration. Further, Estragole gives protection against bacteria and viruses. The objective of this review was to briefly discuss the natural sources of Estragole, its chemistry, its extraction, its bioavailability, absorption, distribution, toxicity, and carcinogenicity, and its biomedical effects in vivo or in vitro are discussed in this review. The market for Estragole, as well as its regulatory framework also explained in this study.

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Introduction

Essential oils are complex substances with a strong odor and are volatile. Terpenes, oxidizing chemicals, and fatty compounds in essential oils impact their qualities, which are widely utilized in food, perfumes, cosmetics, pesticides, herbicides, traditional remedies, sedatives, diuretics, expectorants, and digestion (1). Estragole is one of the relatively nontoxic terpenoid ethers and has broad applications for aromatherapy and treatment compared to other essential oils (2). In addition, Estragole is a eugenol derivative widely used through chemical synthesis pathways for new alternative drugs (3). Estragole is a monoterpene extracted from natural ingredients such as basil, star anise, anise, and fennel. Additionally, plant environmental conditions, harvest time, storage, and extraction affect the amount of estragole obtained (4), and Estragole exhibits anesthetic, sedative, antimicrobial, antioxidant, anticonvulsant, and macrophage phagocytic and leukocyte activity (5). Research on Estragole has been done before (6,7). However, in research, it is necessary to distinguish between Estragole as a single substance or in the complex herbal extract form (8). Therefore this study aims to determine the therapeutic properties of Estragole by observing its sources, chemistry, extraction, bioavailability, absorption, distribution, and effect on animal health toxicity and carcinogenicity either singly or extracted from plants.

Sources and chemistry of estragole

Estragole is a volatile phenylpropanoid that belongs to the alkylbenzene group. This group includes myristicin, isosafrole, methyl eugenol, anethole, eugenol, safrole, isoeugenol, apiole, and elemicin (9). Estragole compounds could be extracted from plants (Figure 1), especially basil (*Ocimum basilicum*), ravensara (*Ravensara anisata*), fennel (*Foeniculum vulgare*), tarragon (*Artemisia dracunculus*), Korean mint (*Agastache rugosa*), Illiciaceae (*Illicium anisatum*), Canela de cunhã (*Croton zehntneri*), and Apiaceae (*Pimpinella anisum*) which are widely processed for the food, beverage and flavoring industries, detergents, soaps, and perfumes (5,10). Estragole is a colorless compound, smells of anise, and is insoluble in water. The chemical class of Estragole is alkylbenzenes, with a molecular weight of 148.20. Its molecular formula is $C_{10}H_{12}O$, and its Chemical Abstracts Service (CAS) is 140-67-0. Its flash point is 81˚C, and its density is 0.965 g/L, with a boiling point of 215-216˚C. Furthermore, it has many synonyms such as esdragon, esdragol, Estragole, tarragon, isoanethole, p-allylanisole, 4-allylanisole, 1-allyl-4-methoxybenzene, 4-allyl methyl benzene, 1-methoxy-4-prop-2-enyl benzene, 1-methoxy-4-(2-propenyl) benzene, 3-(p-methoxyphenyl)propane, p-methoxy allylbenzene, methyl chavicol, chavicyl methyl ether, o-methyl chavicol, chavicol methyl ether, dan NCI-C60946 (11).

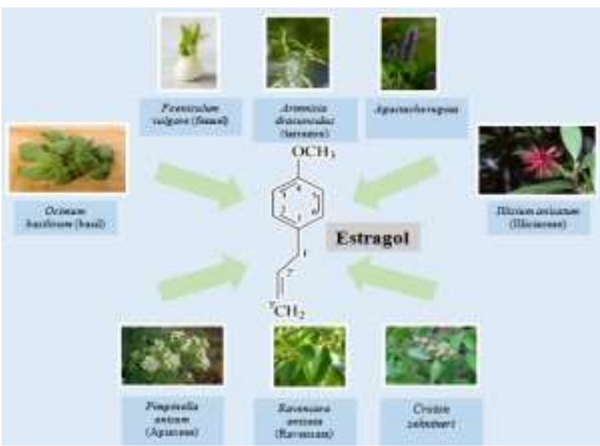

Figure 1: Natural sources of Estragole

In anethole, the double bond of the propenyl side chain is conjugated to the aromatic ring, but in Estragole, it is unconjugated (12). Another difference is that Estragole could form homobenzylate radical cations, while trans-anethole could form conjugated radical cations. In addition, trans-anethole has dimerization by forming an intermediate radical cation, whereas Estragole does not (13-15).

Estragole extraction

Estragole is commonly obtained by extracting plants containing a compound in the form of phenylpropene consisting of anethole, monocyclic monoterpene hydrocarbon limonene, and bicyclic oxygenated monoterpene fenchone (16). Espagnole could be extracted from plants such as fennel by 2 methods, namely Soxhlet or Accelerated Solvent Extraction (ASE), in which the Soxhlet method provides better and more abundant extraction results compared to ASE. The solvents used in the extraction are polar protic solvents such as methanol and ethanol, in which methanol gives a higher extraction yield than ethanol. For example, in fennel extraction, methanol solvent could produce 87-89% estragole, while ethanol produces 86-87% estragole (17).

Estragole may be extracted from *Agastache rugosa* using Headspace Solid Phase Microextraction (HS-SPME) or gas chromatography-mass spectrometry (GC-MS) methods, which could provide 95 percent estragole extraction (10). Moreover, in basil, the method for extracting Estragole could use Microwave-Assisted Hydro-Distillation (MAHD), which is then improved by Response Surface Methodology (RSM) and analyzed by GC-MS. The yield of estragole extraction could reach 87.869% depending on size, water ratio, time, and wave power used in basil (18). Another technique used to increase the phytochemical and antioxidant activity of Estragole in basil is gamma-radiation (19-21). Commonly, irradiation is used as a treatment technique such as heating, cooling, high pressure, and fumigation (21).

Estragole bioavailability, absorption, and distribution

When Estragole enters the digestive tract, its metabolism occurs, especially within the liver (22). Estragole's allylic side chain is broken down by mixed-function oxidase into three compounds: estragole 2',3'-oxide, 1'-hydroxyestragole, and 4-methoxycinnamate alcohol. After a spontaneous breakdown, SULTs convert 1'-hydroxyestragole to 1'-sulfooxyestragole by releasing carbocations that can bind to proteins and DNA (Figure 2). However, it has a negative effect by inducing carcinogenesis (9). Meanwhile, 4-methoxycinnamyl alcohol is oxidized to 4-methoxycinnamic acid and 4-methoxy benzoic acid. In the compound Estragole-2',3'-oxide, it is converted to 2',3'-dihydroxy-4-propylanisole, followed up by epoxide hydrolase, then further oxidized to 4-methoxyphenylacetic acid and 4-methoxyphenyllactic acid (11). In addition, in rodents and humans, there is another estragole metabolic pathway, namely O-Demethylation, in which the O-demethylation pathway shifts to 1'-hydroxylation (23).

Effect of estragole on the animal production

During animal growth, estragole supplementation could increase body weight (24,25). Previous study reported that supplementing *Ocimum gratissimum* leaf extracts containing Estragole as the main ingredient in broiler chickens increases growth, preserves blood components, and reduces harmful microorganisms in the intestine that could stimulate inflammation for finishing broilers (26). The birds without the extracts had higher microbial loads, indicating that *Ocimum* had antimicrobial properties. Moreover, experiments El-Naggar and El-Tahawy (27) used broilers treated with basil extract (0.1, 5, and 20 g/Kg body weight) for 39 days, indicating that body weight (BW) increased significantly. Furthermore, supplementation of basil seeds and leaves (0.8% estragole in the herb) might enhance feed intake (FI), feed efficiency, and average daily gains (ADG) (28-30). The increased FRC in herbal-based feeds is due to increased protein digestibility in the small intestine (31). Meanwhile, supplementation with dried basil leaves could increase the relative weight of broiler organs such as the liver, gizzard, and heart (29). In sheep, supplementing a 6% fennel by-product containing Estragole (9.79g/100g) could increase FCR and ADG (30). Lately, in rabbits, the administration of fennel (3.5-12.0% estragole in essential oil) could improve their nutrient digestibility, nutritive values, ADG, FCR, and increase antioxidant enzymr production (31). Estragole also exhibited a notable antistress effect against stress (32). Estragole supplementation in rats of 50 - 200 mg/kg body weight increased urinary VMA and ascorbic acid excretion. VMA and ascorbic acid levels in mice might be used to assess antistress activity. As a result, Estragole may work as an antistress agent (33). However, a study by Riyazi *et al.* (34) indicated that supplementation with the *O. gratissimum* in the starter and grower diets (200, 400, and 600 ppm) of broilers had a non-significant influence on the FI, ADG, and FCR. Meanwhile, the experiment conducted by Abbas (30) showed that 3 g/kg bacillus sp. dietary did not affect carcass train and viscera organ. Also, the effects of fennel seeds (*F. Vulgare Mill*.) (1.5-5.0% estragole in essential oil) supplementation on the production performance of Japanese quail (*Coturnix japonica*) exhibited no significant differences in initial body weights (35). While according to Abbas *et al.* (28), Basil essential oil may enhance total protein (4.21 mg/Kg), globulin (2.62 mg/Kg), albumin (4.21 mg/Kg), and reduce total *E. coli* bacteria (4.07 x 10^3) and total fungi (4.46×10^3). In summary, Estragole could improve broiler performance by enhancing growth performance through increasing BW, ADG, and FI and providing favorable FCR. However, further studies need to be conducted on other animals to determine the effect of Estragole on animal performance.

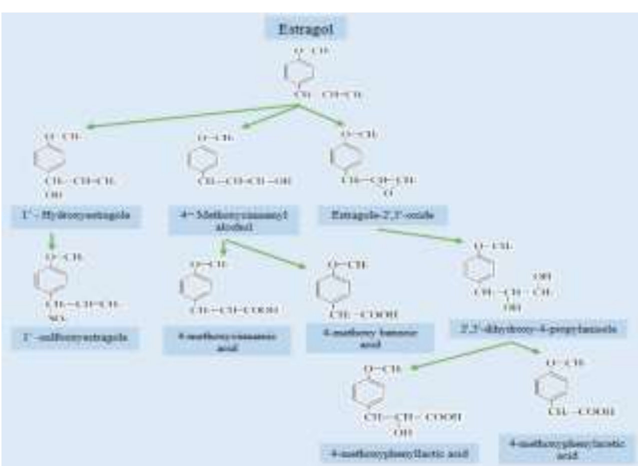

Figure 2: Estragole metabolism and carcinogenesis-related pathways.

Antioxidant effect of estragole

Several studies show that Estragole has antioxidant, anti-inflammation, antibacterial, and antiviral properties that benefit animal health (Figure 3 and Table 1). Junior *et al.* (36) observed that estragole supplementation positively influenced antioxidant status by preserving GSH and GPx and could reduce MPO and MDA activity, which may minimize lipid peroxidation products and reactive oxygen species, which could also reduce gastrointestinal damage (37,38). Meanwhile, MDA indicates oxidative stress and lipid peroxidation that could accumulate in gastrointestinal inflammation and ulcerated lesions (37-39). Another free-radical builder is MPO which is a marker of neutrophil infiltration. Besides, chloramine is associated with pro-inflammatory responses and oxidative damage (40,41).

The antioxidant activity of fennel extracts in the aqueous-alcoholic mixture is attributed to the presence of Estragole, which may block the peroxidation of the linoleic acid system (42,43). Moreover, fennel also can increase SOD, HDL, and catalase activity and decrease MDA (44). DPPH radical scavenging activity was remarkable in *F. vulgare var. Azoricum* (12% estragole in essential oil), even greater than ascorbic acid and BHT. Meanwhile, *F. Vulgare var. dulce* (6% estragole in essential oil) had scavenging efficacy comparable to ascorbic acid and BHT. Furthermore, the cultivar *F. Vulgare var. Vulgare* exhibits 37 - 44 times the radical scavenging activity of azoricum or dulce cultivars (13).

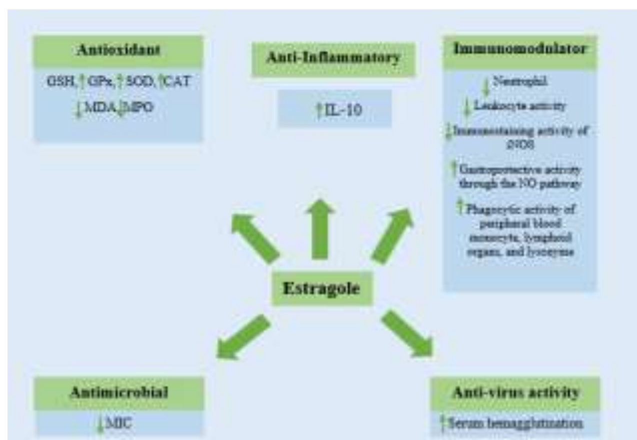

Figure 3: Biomedical applications of estragole.

The source of free radical scavengers in basil (*O. basilicum*) comes from Estragole which could reach 87.869%. Basil supplementation could improve antioxidant status by increasing GSH, SOD, and CAT and decreasing lipid peroxidation (MDA) (45). Arya *et al.* (46) discovered that bacillicum might restore the activity of GPx, SOD, and CAT in cardiac tissue after myocardial necrosis while lowering MDA levels. *O. basilicum* also dramatically restored the GSH content changes caused by global ischemia and reperfusion. (19). But, in extract form, basil significantly decreased MDA, SOD, GPX, and CAT concentration (47).

In rats, gamma irradiation of basil water extract could reduce oxidative stress initiated by arsenic (45). The antioxidant effect of basil in mice could also increase MDA levels in brain tissue and protect brain cells from harmful effects (47,48).

In addition, Kahlo *et al.* (49) concluded that feeding *O. basilicum* leaves powder to broilers was found to have good antioxidant and immunostimulant effects against gibberellic acid and auxin through the antioxidant effect of SOD, CAT, GSH, GPx, and GST. In summary, supplementing Estragole as a single substance and from plant extracts could positively affect animal antioxidant capacity by increasing GSH, GPx, SOD, and CAT, also reducing MDA and MPO.

Anti-inflammatory and immunomodulatory effect of estragole

Estragole is a significant chemical component of *Ocimum basilicum*, increasing anti-inflammatory (50). In an in vitro chemotaxis test, Silva-Comar *et al.* (5) discovered that Estragole might prevent neutrophil migration toward fMLP. Meanwhile, fMLP is a chemotactic drug that promotes the production of cytokines, including IL-1 β, IL-8, and TNF-α (51). Moreover, Estragole could decrease the number of attached or rolling leukocytes going to the perivascular tissue in an in vivo microcirculation test. When inflammation occurs, leukocytes will quickly go to the site of the lesion through the postcapillary venules through transmigration, rolling, and adhesion (52,53). However, when leukocytes migrate in a persistent state, it could initiate tissue damage because they could release nitrogen and reactive oxygen metabolites and proteolytic enzymes (54). Furthermore, Silva-Comar *et al.* (5) demonstrated that Estragole possessed potential anti-inflammatory properties, most likely by blocking leukocyte migration and increasing macrophage phagocytosis.

The previous research by Ponte *et al.* (55) concluded that estragole supplementation in rats could reduce paw oedema due to the presence of TNF-α. According to Oliveira *et al.* (56), Estragole has an anti-inflammatory activity that could decrease paw oedema activity. Júnior *et al.* (36) also showed that levels of pro-inflammatory cytokines could be lowered by estragole supplementation and could also increase IL-10. Estragole could also affect other substances, such as nitric oxide (NO), P, cytokines, bradykinin, serotonin, and histamine (55). Júnior *et al.* (36) reported that Estragole could also play a role in gastroprotective activity through the NO pathway, which could be inhibited by NOS, thereby reducing gastroprotective activity. Estragole could also decrease the immunostaining activity of iNOS, which indicates that it has immunomodulatory activity. Furthermore, Estragole has been demonstrated to exhibit antinociceptive and anticonvulsant effects in vivo, which have been linked to GABAAR regulation (57,58).

According to Farida and Nahid (59), adding *Ocimum basilicum* leaves powder to broiler chicken feed improves the innate immune response, as seen by considerable improvements in cells' phagocytic activity of peripheral blood monocyte, lymphoid organs, and lysozyme concentrations. According to ELnaggar and El-Tahawy (60), Adding *Ocimum basilicum* leaves powder or seed oils to the broiler basal diet boosted the phagocytic index and activity of the macrophages, allowing it to be administered effectively as a natural growth promoter to improve broiler chick development and immunological response. In addition, oral treatment of aqueous and ethanolic leaf extracts of *O. basilicum* in mice resulted in a considerable rise in the carbon clearance index in mononuclear macrophages, indicating an improvement in phagocytic function and nonspecific immunity (61). Additionally, *O. basilicum* essential oil has been shown to lower the overall number of leukocytes, monocytes, granulocytes, and lymphocytes (50).

Supplementation of Estragole as a single substance and from plant extraction could positively affect anti-inflammatory and immunomodulatory agents in animals by increasing IL-10, preventing neutrophils, decreasing leukocyte activity, and the immunostaining activity of iNOS. Also, preserve gastroprotective activity through the NO pathway and improve the phagocytic activity of peripheral blood monocyte, lymphoid organs, and lysozyme concentrations.

Antimicrobial and anti-virus activity

Estragole also has antibacterial activity but is relatively minor compared to cinnamaldehyde (13). The antibacterial activity of Estragole compared to cinnamaldehyde was more robust in the liquid culture test but lower in the vapor diffusion test. Estragole was also reported to have the effect of lowering the antibiotic MIC and positively influencing the action of erythromycin RN4220 S. aureus strain (62). Coêlho *et al.* (63) showed that combined at sub-inhibitory concentrations. Estragole could decrease norfloxacin's MIC, which can induce SA1199-B S. aureus infection by pumping Nora. Accordingly, Estragole does not directly affect bacterial growth but could reduce MIC when associated with erythromycin, which exhibits an antibiotic effect.

Mohamad and Abasali (64) found that *O. basilicum* extracts in a diet mixture enhanced lysozyme activity in common carp and significantly augmented fish's immune systems to avoid and control microbial diseases. Therefore, *E. coli* growth could also be reduced by supplementation of basil essential oil (35). Meanwhile, Naksang *et al.* (65) discovered that *O. basilicum* leaves powder had high antibacterial action towards foodborne infectious Gram-positive bacteria, specifically *Bacillus cereus* and *Listeria monocytogenes*, as well as *S. aureus*. Therefore, *E.coli* infection could also be reduced by supplementing basil essential oil and in *S. Typhimurium* and *C. perfringens* (66-68).

Table 1: Effect of Estragole on animal

Animal	Dose Rate	Major Findings	Ref
Mice	Oral estragol supplementation at a dosage of 100 mg/kg	Enhance humoral and immune responses of mice infected with *T. gondii*	(56)
Mice	Estragole was taken orally at a dosage of 30 mg/kg.	Inhibits peritoneal vascular permeability and leukocyte emigration.	(50)
Mice	Oral estragol supplementation at a dosage of 250-750 mg/kg	The anti-inflammatory activity of Estragole was demonstrated by stimulating macrophage and phagocytic activity and inhibiting leukocyte recruitment	(5)
Dog	Powdered basil (*Ocimum basilicum*) leaves are mixed with dog food at a dosage of 0.025-0.05%	It may prevent DM by modulating blood glucose and improving antioxidant status in Rottweiler dogs.	(93)
Chicken	Chicks fed a normal diet supplemented with 1 % - 0.5 % OBLP (*Ocimum basilicum* leaves powder)	Increased HI antibodies to NDV vaccines and show anti-oxidative activity	(94)
Chicken	970 g corn silage per kilogram, combined with 30 g dried basil per kg (*Ocimum basilicum*)	Increased egg production	(95)
Broiler	In drinking water, broilers supplemented with 5 ml/kg *Ocimum basilicum* + 75 ppm GA3 (Gibberellic Acid) or 75 ppm IAA (Indol Acetic Acid).	Basil dramatically enhanced IgG and IgM antibody levels as well as antioxidant activity (SOD, CAT, GSH, GPx, GST)	(49)
Broiler	Broilers supplemented with basil (*Ocimum basilicum*) flour in feed up to 3%	Reduced the mortality in broiler chickens and excreta NH_3 and H_2S gases	(50)
Broiler	Basal diet supplemented with 5 g/kg basil seed (*Ocimum basilicum*) and 200 mg/kg ascorbic acid.	Improved intestinal villus, increased crude protein (CP), crude fiber (CF), and metabolized energy absorption (ME). Increase white blood cell count, hemoglobin, antibody titer to new castle disease, weight growth, and feed conversion ratio.	(51)
Broiler	Basal diet supplemented with basil leaves (*Ocimum gratissimum*) 5 - 15 g/bird	Increased FCR, weight, and total feed consumption	(52)
Broiler	The base food was treated with 0.3 mL of fennel oil per kg body weight.	Increase phagocytic index, phagocytic activity, leukocytes, globulins, heterophils, total protein, A/G ratio, T3, T4, IgM, and IgG	(53)
Broiler	Feed was added with 0.30% fennel seed powder (*Foeniculum vulgare Mill.*)	Improved intestinal morphology and promotion of healthy and effective development	(54)
Broiler	Basal diet supplemented with 3.2% fennel seeds	Fennel seed powder could be used to enhance the broiler's tolerance during chronic heat stress conditions.	(55)
Quail	Basal diet supplemented with basil (*Ocimum basillicum L.*) essential oil 250 - 500 mg/kg.	Increase body weight, feed intake, quail FCR, total protein, globulin, and albumin, and decrease the overall quantity of dangerous bacteria and the total number of fungi.	(28)
Quail	Basal diet supplemented with fennel seeds supplemented at 1% of their body weight.	Improved mean body weight	(35)
Sheep	The animals are fed a diet consisting of a 50% sweet basil (*Ocimum basilicum* L.) by-product and a 50% concentrate feed combination.	Improved nutrient digestibility, body weight increase, growth performance, and feed efficiency	(96)
Lamb	Supplemented with fennel (*Foeniculum vulgare*) seed powder 1.5% in feed	Increases testosterone concentration, muscle tissue, and FCR	(97)
Lamb	Feed added 0.75% - 1.5% *Foeniculum vulgare*	Increase yield, quality, the composition of meat and also increase fat oxidation	(98)
Calves	Starter diet with 0.4 percent fennel powder	Increases the molar percentage of rumen propionate, speeds up weaning time, and improves calf performance	(99)
Rabbit	A standard diet supplemented with 400 mg of essential oil of basil (*Ocimum basilicum*) (BO)	The serum total antioxidant capacity increased, and the malondialdehyde level decreased compared to the control group.	(100)
Rabbit	Basal diet supplemented with 40% fennel seeds	They improved their nutritional digestibility, nutritive values, ultimate body weight, average daily growth, feed conversion ratio, and mortality rate while achieving the best relative economic efficiency value.	(31)
Shrimp	Fed with 1.0 - 5 g (*Ocimum basilicum*)/kg	Improved growth and tolerance to infection with V. parahaemolyticus	(32)
Guppy	Fennel was supplied twice daily at 3% of their body weight.	Increased fertility rate	(101)

Moreover, Ivanov *et al.* (69) showed that the A*gastache foeniculum* composed of 93.45% estragole produced a MIC of 1.25 L/ml on the growth of S. aureus (ATCC 25923) and other gram-positive bacteria. Estragole, the main volatile ingredient in *A. rugosa* essential oils, may be responsible for their phytotoxic and antibacterial properties (70).

Estragole is likewise a significant component of the subspecies *Vulgare*, which has a practical antibacterial impact on methanogenic bacteria development (17). For example, Shahat *et al.* (13) showed that oil from *F. Vulgare azoricum* was more efficient than ampicillin against Gram-negative bacteria, including *E.coli* and *Pseudomonas aeruginosa*, by 25% and 7%, respectively. Meanwhile, compared to ampicillin, the essential oil of *F. vulgare* Vulgare could combat Gram-positive bacteria such as *S. aureus* and *Bacillus subtilis* by 58.3 percent and 114 percent, respectively.

The effectiveness of Estragole against virus infection was reported by Farida and Abdulaziz (59). They found that supplementation of *O. basilicum* seeds in broiler diets significantly increased the serum hemagglutination inhibition antibody titers and eliminated Infectious Bronchitis Viruses (IBV) and Newcastle Disease (ND). Meanwhile, Haiyan (62) showed antiviral activity of *F. Vulgare* essential oil against parainfluenza virus type-3 (PI-3) RNA and Herpes simplex virus type-1 (HSV-1) DNA. In conclusion, supplementing Estragole as a single substance and from plant extracts may improve antiviral and antimicrobial activity by lowering serum hemagglutination, or MIC, of gram-positive and detrimental bacteria. MIC is the least amount of a chemical, usually a drug, that prevents the growth of bacteria or visible bacteria.

Toxicity and carcinogenicity of estragole

Estragole's carcinogenicity is caused by a genotoxic mechanism (11). Estragole may operate as a genotoxic hepatocarcinogen in rodent liver by producing DNA adducts responsible for Estragole's genotoxicity (71). Genotoxicity occurs due to estragole metabolism in the liver by cytochrome P450, which results in 1'-hydroxy Estragole and certain DNA-reactive epoxides (72). Moreover, due to its subsequent activation to 1′ -sulfoxyestragole by sulfotransferases, 1′ -hydroxyestragole was primarily responsible for the observed genotoxic impact (73). The spontaneous cleavage of sulfate produces an allylic carbocation, rapidly forming covalent connections with proteins and DNA (74).

Estragole epoxides, namely estragole-2',3'-oxide and 1'-hydroxy estragole-2',3'-oxide, have also been demonstrated in vitro to be hepatocarcinogenic and to form DNA adducts (72-75). On the other hand, Estragole epoxide has a modest function in tumorigenicity, and in vivo, estragole administration tests have not discovered the related DNA adduct (76). Meanwhile, epoxide hydrolase enzymes and glutathione S-transferases are more effective and quicker at removing glutathione (77).

When converted to the carcinogenic 10-sulfoxymetabolite, estragol isolated from basil might be carcinogenic and genotoxic (78). Most testing for genotoxicity has yielded negative findings. Martins *et al.* (79) discovered that Estragole's genotoxicity could impact cell death since Estragole only triggers apoptosis after extended incubation durations (more than 18 hours) and only at the maximum dose evaluated (2000 M).

Estragole's toxic impact and negative geotaxis assays on adult *D. melanogaster* flies have also been reported to alter mortality, with the flies experiencing damage to their locomotor system and being unable to move in the vertical plane (80,81). Furthermore, the concentration of Estragole in the essential oil of the variety *O. basilicum* varied from 52 to 100 percent and was poisonous to Rhyzopertha Dominica, Sitophilus oryzae, and Cephalotes pusillus, indicating that Estragole might limit growth (82,83).

On the other hand, Estragole did not generate chromosomal aberrations (CAs) in V79 Chinese hamster cells, whether exogenous biotransformation systems were present or not. Estragole shows no toxicity in mice consuming low doses of food-containing compounds (84,85). Moreover, in the study by Schulte-Hubbert *et al.* (71), incubation of Estragole for 24 hours did not result in significant cytotoxicity. Various literature shows that Estragole has toxicity and carcinogenicity effects, but further studies need to be done to determine the dose that could initiate toxicity and carcinogenicity.

Market and regulatory issues of estragole

Estragole is an essential oil ingredient and a position isomer of monoterpenes utilized in medicinal formulations, flavorings, and alcoholic drinks (86). Estragole has been certified safe by the United States Food and Drug Administration (FDA-US)(87). Estragole and essential oils from fennel, anise, tarragon, basil, and bay leaves are listed as safe for eating by the US Department of Food and Agriculture (88). Meanwhile, the Flavor and Extract Manufacturers Association (FEMA) Expert Panel maintains that intake of estragole and estragole extract from plants is safe and does not initiate cancer risk based on evidence of nonlinear interactions, covalent bonding, metabolism, and metabolic activity (89).

In 1990, 1994, and 1998 it was reported that the production of Estragole in the US reached one million pounds per year (90). Estragole also plays a role in promoting economic development by increasing the production of chemicals (91). However, the Committee of Experts on Flavouring Substances (CEFS) identified Estragole as a naturally found genotoxic carcinogen in experimental animals following either chronic or a few repeated exposures in 2000 (89). Furthermore, the Scientific Committee on Food recommends limiting the supplementation of Estragole because it is known to have carcinogenic and genotoxic effects (92). Estragole has been widely used for various products for both human and animal needs, but its direct use needs to be taken into account due to the effects of toxicity and carcinogenicity.

Conclusion

This review explains natural sources, chemistry, extraction, bioavailability, absorption, distribution, toxicity, and biological effects, also market and regulatory issues of Estragole. Estragole has several medicinal uses, including antioxidant, anti-inflammatory, antibacterial, and antiviral properties. Estragole's biological actions might be ascribed to its high antioxidant capability and anti-inflammatory activity through boosting cytokine release. In addition, there is still debate about the carcinogenic effect of Estragole. Therefore, further detailed research is required to understand the safety of Estragole.

Conflict of interest

There is no conflict of interest in this study.

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إستراكول: مراجعة للتأثير الدوائي وتاثيره على صحة الحيوان وادائه وتاثيره السمي والمشاكل التنظيمية التسويقية

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فرع الصحة، كلية الدراسات المهنية، جامعة إيرلانجا، سورابايا، إندونيسيا[١]، مدرسة التقنية الحيوانية والابتكار، جامعة سوراناري للتكنولوجيا، ناخون راتشاسيما، تايلاند[٢]، قسم السريريات البيطري، كلية الطب البيطري، جامعة إيرلانجا، سورابايا، إندونيسيا[٣]

الخلاصة

استراكول هو جزيء تربينويد متطاير يتواجد في مختلف النباتات أو المكونات وغالبًا بتركيزات عالية جدًا. لقد ثبت أنه يزيد من صحة الحيوان وأداء المخرجات بشكل فعال. لقد ثبت أن الإستراغول يمتلك خصائص مضادة للأكسدة في المختبر وفي الجسم الحي. تشمل هذه الخصائص القدرة على رفع مستويات الكلوتاثيون والكلوتاثيونبيروكسيداز، بالإضافة إلى القدرة على قمع المواد السامة والحفاظ على حالة الأكسدة الخلوية ونشاط المالونداياالديهايد والمايبلوبيروكسيداز. بالإضافة إلى ذلك، فإنه ينتج تأثيرات مضادة للالتهابات ومعدلة للمناعة من خلال إنتاج وإطلاق السيتوكينات، والمادة P، والبراديكينين، والهستامين، والسيروتونين، والسيتوكينات، وأكسيد النيتريك (NO)، ويؤدي إلى هجرة كبيرة للكريات البيض علاوة على ذلك، يوفر استراكول الحماية ضد البكتيريا والفيروسات. كان الهدف من هذه المراجعة هو مناقشة المصادر الطبيعية للإستراكول و كيميائيته واستخراجه و توافره الحيوي وامتصاصه وتوزيعه وسميته ومسبباته للسرطان واثاره الطبية في الجسم الحي او في المختبر. كذلك تم من خلال هذه المراجعة توضيح سوق الاستراكول وكذلك إطاره التنظيمي.