

(REVIEW ARTICLE)



Constituents and therapeutic activities of *Pimpinella anisum*: A review

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Abstract

Pimpinella anisum (Apiaceae), is indigenous to Near East and widely cultivated in the temperate regions. The fruits of *Pimpinella anisum* were used traditionally as a spice for flavouring bread and bakery products, and the essential oil was added to foodstuff and liqueurs as a sensory and flavoring agent. It was listed as a natural source of feed flavouring by the Council of Europe. Medicinally, the fruits were used as expectorant, digestive, antispasmodic, carminative, parasiticide, for bronchial catarrh, pertussis, spasmodic cough, spasmodic gastrointestinal complaints, to increase milk secretion, to promote menstruation, to facilitate birth, to alleviate symptoms of the male climacteric, to increase libido and externally for pediculosis and scabies. The recent studies showed that *Pimpinella anisum* possessed Antioxidant, hepatoprotective, nephroprotective, antihypertensive, hypolipidemic, Antiinflammatory, antimicrobial, antiparasitic, antidiabetic, local anesthetic, anticonvulsant, hypnotic, antidepressant, anxiolytic, anti-cholinesterase, neuroprotective, immunomodulatory, anticancer, laxative effects and increased milk production, prevented osteoporosis and minimized premenstrual syndrome. The current review was designed to highlight the chemical constituents and pharmacological effects of *Pimpinella anisum*.

Keywords: *Pimpinella anisum*; Anise; Constituents; Pharmacology; Toxicology

1. Introduction

In the last few decades there has been an exponential growth in the field of herbal medicine. It is getting popularized in developing and developed countries owing to its natural origin and lesser side effects. Furthermore, two thirds of the new chemicals identified yearly were extracted from higher plants. 75% of the world's population used plants for therapy and prevention. In the US, where chemical synthesis dominates the pharmaceutical industry, 25% of the pharmaceuticals are based on plant-derived chemicals⁽¹⁾. Plants generally produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of many pharmaceutical drugs⁽²⁻⁸⁾. This review presented a comprehensive overview of the phytochemical and pharmacological profile of *Pimpinella anisum*, it was used for therapeutic purposes as traditional medicine across the world by various cultures.

1.1. Synonyms

Anisum odoratum, *Anisum officinale*, *Anisum officinarum*, *Anisum vulgare*, *Apium anisum*, *Carum anisum*, *Pimpinele anisa*, *Ptychotis vargasiana*, *Selinum anisum*, *Seseli gilliesii*, *Sison anisum*, *Tragium anisum*⁽⁹⁾.

1.2. Taxonomic classification

- **Kingdom:** Plantae,
- **Subkingdom:** Viridiplantae,
- **Infrakingdom:** Streptophyta,
- **Superdivision:** Embryophyta,

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- **Division:** Tracheophyta,
- **Subdivision:** Spermatophytina,
- **Class:** Magnoliopsida,
- **Superorder:** Asteranae,
- **Order:** Apiales,
- **Family:** Apiaceae,
- **Genus:** *Pimpinella*,
- **Species:** *Pimpinella anisum*⁽¹⁰⁾.

1.3. Common names

- **Arabic:** Anison, Yanson; Chinese: hui qin,
- **English:** anise, sweet cumin;
- **French:** anis, anis vert;
- **German:** Anis;
- **Italian:** anice, anice vero;
- **Portuguese:** anis, erva-doce;
- **Spanish:** anis;
- **Swedish:** anis⁽¹¹⁾.

1.4. Distribution

It was indigenous to Near East and widely cultivated in the temperate regions ⁽¹²⁾.

1.5. Description

Annual herb, 10–50 cm, sparsely shortly pubescent throughout, strongly aromatic. Taproot slender. Stem much-branched. Leaves heteromorphic. Basal leaves simple; petioles 2–5 cm; blade reniform or broad-ovate, 1–3 × 1.2–2.8 cm, puberulent along veins, margin serrate. Cauline leaves 1–2-pinnate; ultimate segments ovate or ovate-lanceolate, 6–17 × 2–7 mm, 3-lobed margin serrate or lacerate. Leaves reduced upwards, becoming 3-lobed; lobes lanceolate or linear-lanceolate. Umbels 1.5–6 cm across; bracts 1(or 2) or absent, linear-lanceolate, 1–2 mm; rays 7–15, 1–4 cm, unequal; bracteoles 1(or 2) or absent, linear, 2–3 mm; umbellules 5–10 mm across, ca. 10-flowered; pedicels 2–6 mm, extending to 10 mm in fruit. Calyx teeth obsolete. Petals white, obcordate, abaxially pubescent, apex with incurved lobule. Stylopodium conic; styles ca. 3 × stylopodium, ca. 0.5 × fruit, spreading or reflexed. Fruit oblong-ovoid, 3–5 × 2–2.5 mm, densely appressed setose-hairy; vittae 2–4 in each furrow, 4–8 on commissure, nearly forming a continuous ring around seed ⁽¹³⁾.

1.6. Traditional uses

For long time the fruits of *Pimpinella anisum* were used traditionally as a spice for flavouring bread and bakery products, and the essential oil was added to foodstuff and liqueurs as a sensory and flavoring agent. It was listed as a natural source of feed flavouring by the Council of Europe, and was listed as Generally Recognized as Safe (GRAS) in USA ⁽¹⁴⁻¹⁵⁾.

The fruits were used as expectorant, digestive, antispasmodic, carminative, parasiticide, for bronchial catarrh, pertussis, spasmodic cough, spasmodic gastrointestinal complaints, to increase milk secretion, to promote menstruation, to facilitate birth, to alleviate symptoms of the male climacteric, to increase libido and externally for pediculosis and scabies ⁽¹⁵⁾.

However, anise and its essential oil are globally used in food, medicine, perfumery, and cosmetic industries ⁽¹⁶⁾.

1.7. Parts used medicinally

The seeds and essential oil ⁽⁶⁾.

1.8. Chemical constituents

The preliminary phytoanalysis of *Pimpinella anisum* seeds showed the presence of carbohydrate derivatives, amino acids, polyphenols, flavonoids, tannins, steroids, terpenoids and saponins ⁽¹⁷⁾.

Seeds contained moisture: 9-13%, protein: 18%, fatty oil: 8-23%, essential oil: 2-7%. starch: 5%, N-free extract: 22-28%, crude fibre: 12-25%. Essential oil yielded by distillation is generally around 2-3% and anethole makes up 80-90% of the oil⁽¹⁸⁾.

The methanolic extract of the seeds contained total phenolics (502.7±1.1mg/100 GAE), total flavonoids (221.7±0.7 mg/100 RE) and tannins (53.2±0.6 mg/100 CE) ⁽¹⁹⁾.

Six polyphenols (apigenin, caffeic acid, chlorogenic acid, luteolin, rutin and quercetin) were identified in the ethyl acetate fraction of *Pimpinella anisum* seeds, while, apigenin, luteolin, quercetin and rutin were identified in methanolic extract ⁽¹⁷⁾.

However, phenolic acid: gallic acid, chlorogenic acid, caffeic acid, syringic acid, *p*-coumaric acid, rosmarinic acid, ellagic acid; and flavonoids: rutin, quercetin, naringin, apigenin, larcitrin and cirsimartin were isolated from the seeds of Tunisian and Egyptian anise ⁽²⁰⁾. Seeds also contained coumarins (umbelliferone, umbelliprenine, bergapten, and scopoletin)⁽²¹⁾.

The major constituent of the oil of *Pimpinella anisum* seeds from Giessen- Germany, was trans-anethole (82.1%) followed by γ -himachalene (7.0%) ⁽²²⁾.

The main compounds isolated from the oil of aniseed from North part of Serbia, was trans-anethole (96.80%) and γ -himachalene (1.84%) ⁽²³⁾.

The major oil constituent of *Pimpinella anisum* from Alberta, was trans-anethole 57.4% of whole plant oil, and 75.2% of seed oil, followed by cis-anethole, carvone, β -caryophyllene, dihydrocarvyl acetate, estragole and limonene which present in a concentration of 1-5% ⁽²⁴⁾.

Iraqi *Pimpinella anisum* showed that the major constituents of the essential oil were anisole (87.99%) followed by estragole (3.01%), and all other components were presented in less than 2%⁽²⁵⁾.

Tunisian and Egyptian anise seed oil contained *trans*-anethole (94.30 and 90.41%) as a major component, followed by γ -himachalene (2.32 and 1.08%), respectively ⁽²⁰⁾.

The main content of the oil of *Pimpinella anisum* from Iran was trans-anethole 89.24%, followed by γ -himachalene 2.89%, methyl chavicol 2.72% and limonene 1.88% ⁽²⁶⁾. Trans-anethole (83.67%), fenchone (5.29%) and 1,2-diisopropenylcyclobutane (6.31%) were the main constituents of the oil of the seeds of *Pimpinella anisum* from Bangladesh ⁽²⁷⁾. The major component of the essential oil of the seeds of *Pimpinella anisum* from Turkey was trans-anethole (78.63%- 95.21%), followed by methyl chavicol, α - terpineol and methyl eugenol ⁽²⁸⁾. Saturated fatty acid included capric acid, lauric acid, myristic acid, palmitic acid, stearic acid and arachidic acid, and unsaturated fatty acid included petroselinic acid, oleic acid, linoleic acid and linolenic acid, were identified in the seeds of *Pimpinella anisum*. Palmitic acid (4.90-13.20%) represented the main constituent of saturated fatty acid and petroselinic acid was the major constituent of unsaturated fatty acid (38.40-46.60%) ⁽²⁰⁾.

2. Pharmacological effects

2.1. Antioxidant effect

The IC₅₀ values of DPPH antioxidant activity were recorded at 48.71 and 52.48 mg/ml, in BSRC (Bangladesh Spice Research Centre) and local market seeds cultivars essential oils respectively ⁽²⁷⁾.

The maximum radical scavenging activity of DPPH (91.18%) was observed at a concentration of 40 μ g/ml of oil ⁽²⁹⁾.

The aniseed essential oil showed potent antioxidant activity (DPPH) in concentrations-dependent manner, the highest antioxidant (84.9±0.267%) was recorded at 10000 ppm ⁽²⁵⁾.

The highest radical-scavenging activity (91.3±1.8%) was possessed by the ethanolic extract of seeds at a concentration of 0.3 mg/ml, followed by the aqueous extract of seeds (82.0±1.2%), while, the aqueous extract of aerial parts showed the lowest radical-scavenging activity (39.0±1.7%) at the same concentration ⁽³⁰⁾.

However, the ethanol and dichloromethane extracts of the seeds possessed the highest abilities to scavenge DPPH radical with $IC_{50} = 12.58$ and $16.45 \mu\text{g/ml}$, respectively. Ethyl acetate extract also exerted higher potential to scavenge DPPH radical ($IC_{50} = 18.75 \mu\text{g/ml}$). The lowest antiradical capacity was possessed by hexane extract ⁽²⁰⁾.

2.2. Hepatoprotective effect

The hepatoprotective effect of fruit extract and essential oil of *Pimpinella anisum* was investigated in an experimental model of nonalcoholic fatty liver disease induced in rats using choline-deficient diet for 90 days. The hydroethanolic extract and essential oil significantly reversed the elevated total cholesterol, LDL, and triacylglycerol and elevated the decreased HDL in a dose-dependent manner. Serum levels of AST and ALT and biomarkers of oxidative stress were significantly modified by both treatments. Histological investigation further confirmed that both treatments reduced macrovesicular steatohepatitis ⁽²⁶⁾.

The protective effects of different extracts and essential oil of *Pimpinella anisum* seeds were studied in CCl₄-induced hepatotoxicity in rats. An *in vitro* model were also used to study the effect on cell viability, cellular reduced and oxidized glutathione and lipid peroxidation in HepG2 cells. *Pimpinella anisum* extracts, effectively attenuated CCl₄-induced toxicity in both *in vitro* and *in vivo* models ⁽³¹⁻³²⁾.

2.3. Nephroprotective effect

The nephroprotective effect of the ethanolic extract of *Pimpinella anisum* (300 mg/kg/day for 8 days) against gentamicin-induced nephrotoxicity was investigated in rats. The plasma levels of creatinine, BUN, MDA and the absolute excretion of sodium and potassium were increased in the gentamicin group. The extract significantly reduced the renal markers and improved gentamicin-induced tubule damage ⁽³³⁾.

2.4. Antihypertensive effect

Methanolic extract, ethyl acetate fraction and all the sub-fractions of *Pimpinella anisum* seeds possessed antihypertensive effect mediated by inhibition of angiotensin converting enzyme (ACE). Ethyl acetate fraction being the most potent fraction ⁽¹⁷⁾.

The effects of the aqueous extract of *Pimpinella anisum* seeds on arterial blood pressure (BP) and its mechanism of action were investigated in rats in the absence or presence of atropine, L-NAME and angiotensin II. The extract reduced BP and its effects were not due to diuretic, sympatholytic or parasympathomimetic actions. The extract does not act as an angiotensin receptor blocker and does not induce hypotension by reducing vascular resistance induced by oxide nitric. In the depolarized portal vein, the extract inhibited calcium influx, which indicated that the extract possessed calcium channel blocking effect ⁽³⁴⁾.

2.5. Hypolipidemic effect

Methanolic extract, ethyl acetate fraction and the sub-fractions of *Pimpinella anisum* seeds possessed concentration dependent hypolipidemic effect by inhibiting the activity of HMG-CoA reductase and pancreatic lipase. Ethyl acetate fraction being the most potent fraction ⁽¹⁷⁾.

2.6. Antiinflammatory effect

Methanolic extract, ethyl acetate fraction and the sub-fractions of aniseeds exhibited anti-inflammatory potential by inhibiting denaturation of bovine serum albumin, ethyl acetate fraction of aniseeds being the most potent followed by methanolic extract, and the sub-fractions. Ethyl acetate fraction also inhibited the activities of three inflammatory enzymes (lipoxidase, xanthine oxidase and hyaluronidase) and also possessed xanthine oxidase inhibitory activity ⁽¹⁷⁾.

2.7. Antimicrobial effects

The extracts of *Pimpinella anisum* fruits were tested *in vitro* against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherchia coli* and *Klebsiella pneumoniae*. Only aqueous and 50% (v/v) methanol extract exhibited fair antibacterial activity against the test bacteria, while, acetone and petroleum ether extract didn't inhibit the growth of any of the tested bacteria ⁽³⁵⁾.

The antimicrobial activities of essential oils of *Pimpinella anisum* was studied against *C. perfringens* strain A. Only a bacteriostatic activity was exerted by the oil at a concentration of 10 mg/ml ⁽³⁶⁾.

The antibacterial activity of anise seeds was investigated in experimental listeriosis in mice. 24 % of mice treated with essential oil were recovered and improved ⁽³⁷⁾.

The antibacterial activity of fixed oil was investigated against *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Proteus vulgaris*, and *Salmonella typhimurium*. Fixed oil possessed antibacterial effect against the tested bacteria. *Staphylococcus aureus* showed the highest sensitivity to the fixed oil, while the sensitivity was equal against *B. cereus*, *P. vulgaris*, *S. epidermidis*, and *E. coli*, with minimal effect against *S. typhimurium* ⁽²⁹⁾.

The methanolic extract and essential oils of the seeds of *Pimpinella anisum* were evaluated for antibacterial activities against *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Proteus vulgaris*, *Proteus mirabilis*, *Salmonella typhi*, *Salmonella typhimurium*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The essential oils and methanol extracts revealed promising antibacterial activities against most of the tested pathogens ⁽³⁸⁾.

The minimum inhibitory concentration of aniseed essential oil against *Pseudomonas aeruginosa* isolated from burn wounds was 4000-7000ppm. It possessed excellent antibiofilm activity against *P. aeruginosa* biofilms formation with reduction percentage ranged from 26 - 86.41% in co-treatment assay, while the inhibition potentials for pre-developed biofilm decreased significantly by 100% for the majority of *P. aeruginosa* isolates ⁽²⁵⁾.

The antimicrobial effect of ethanol and water extracts of the seeds and aerial parts of *Pimpinella anisum* was evaluated against *Salmonella typhimurium*, *Escherichia coli*, *Bacillus cereus* and *Staphylococcus aureus*. The largest growth inhibitory zones were caused by the ethanolic extract of the seeds against *Bacillus cereus*, *Staphylococcus aureus*, *Salmonella typhimurium*, and *Escherichia coli*, respectively (21.0±1.2, 18.3±1.5, 9.7±1.2, and 7.0±1.2mm) ⁽³⁰⁾.

The antimicrobial activities of *Pimpinella anisum* seed oil were studied against *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*. The oil showed moderate antibacterial effect against *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* ⁽¹⁸⁾.

The antimicrobial effect of the chloroform, petroleum ether, ethyl acetate, methanol and aqueous extracts of the seeds of *Pimpinella anisum* was tested against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and against *Aspergillus niger* and *Candida albicans*. The petroleum ether, chloroform, ethyl acetate and methanol extracts of *Pimpinella anisum* were active against *Bacillus subtilis* (30-40 mm). The ethyl acetate extract showed moderate effect against *Escherichia coli* (15 mm) and low activity against *Pseudomonas aeruginosa* (13 mm). The methanol extract possessed high activity against *Escherichia coli* (16 mm), low activity against *Pseudomonas aeruginosa* (13 mm). All the tested organisms resisted anise seed aqueous extract ⁽³⁹⁾.

Pimpinella anisum extract showed antibacterial activity against *Helicobacter pylori* which suggested an important role in the treatment of gastrointestinal disorders caused by *Helicobacter pylori* ⁽⁴⁰⁾.

The anise-based bio-adhesive vaginal gels exerted modest activity against *S. aureus* and *S. lutea* with no activity against tested Gramnegative bacteria. It also possessed antifungal activity against *Candida albicans*, *C. glabrata* and *C. Parapsilosis*⁽⁴¹⁾.

The antimicrobial activity of silver nanoparticles (AgNPs) using an aqueous extract of *Pimpinella anisum* seeds was investigated against *Staphylococcus pyogenes*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Salmonella typhi*, and *Pseudomonas aeruginosa*. AgNPs showed significant antibacterial activity against all the tested bacteria. The inhibition zones of AgNP were dose-dependent, and the maximum zones of inhibition were obtained at 50 µl⁽⁴²⁾.

Antifungal effects of fluid extract and essential oil of the fruits of *Pimpinella anisum* were studied against clinical isolates of yeasts and dermatophytes species. The fluid extract possessed antimycotic activity against *Candida albicans*, *C. parapsilosis*, *C. tropicalis*, *C. pseudotropicalis* and *C. krusei* with MIC values of 17-20% (v/v). No activity was noticed against *C. glabrata*. The fruits extract also inhibited the growth of dermatophyte species (*Trichophyton rubrum*, *T. mentagrophytes*, *Microsporum canis* and *M. gypseum*) with MIC values of 1.5-9.0% (V/V). The essential oil exerted strong antifungal activity against yeasts with MIC lower than 1.56% (V/V) and against dermatophytes with MIC lower than 0.78% (V/V) ⁽¹²⁾.

The methanol extract of the seeds of *Pimpinella anisum* was tested for their antifungal effect against *Candida albicans*, *Trichophyton mentagrophytes*, *Microsporum canis*, *Aspergillus niger* and *Epidermaphyton floccosum*. The extract of anise seeds inhibited the growth of all fungi at a concentration of 16 mg/ml, except *Aspergillus niger*⁽⁴³⁾.

The antiviral activity of the essential oils of *Pimpinella anisum* was studied against PVX (potato virus X), TMV (tobacco mosaic virus) and TRSV (tobacco ring spot virus). The essential oils totally inhibit the formation of local lesions at a concentration of 3000 ppm⁽⁴⁴⁾.

Lignin-carbohydrate-protein complexes isolated from a hot water extract of seeds of *Pimpinella anisum* showed antiviral activities against herpes simplex virus types 1 and 2 (HSV-1 and -2), human cytomegalovirus (HCMV) and measles virus. They were interfered with virus adsorption to the host cell surface and directly inactivate viruses. They were also enhanced nitric oxide (NO) production by inducing iNOS mRNA, protein expression in RAW 264.7 murine macrophage cells and enhanced mRNA expression of cytokines including IL-1 β and IL-10⁽⁴⁵⁾.

2.8. Antiparasitic effect

The essential oils of *Pimpinella anisum* was tested for its antiparasitic effect against late third to early fourth instar mosquito larvae of *Culex pipiens*. The essential oils possessed high larvicidal activity with a LC₅₀ <18 mg/l⁽⁴⁶⁾.

2.9. Antidiabetic effect

The antidiabetic effect of aqueous anise extract (500 mg/kg orally once daily, for 7 weeks), in the streptozotocin (STZ)-induced diabetes was studied in rat. The diabetic rats showed significant decrease in body weight and increase in blood glucose and serum amylase levels with marked degenerative changes of both β -cells and acinar cells. Anise extract ameliorated all the examined parameters via its hypoglycaemic and antioxidant properties with subsequent downregulation of apoptosis and autophagy⁽⁴⁷⁾.

Anti-diabetic and hypolipidemic effects were assessed in terms of inhibition of α -amylase, α -glucosidase and HMG CoA reductase and pancreatic lipase activities, while antioxidant activity was studied in terms of scavenging of synthetic radicals ABTS and DPPH. *In vivo* studies in diabetes patients by the supplementation of aniseeds (5g/day) for 60 days proved that aniseeds possessed anti-hyperglycemic, hypolipidemic and anti oxidative as evidenced by decreased blood glucose, lipid profile, lipid peroxidation and protein oxidation in aniseed-treated diabetes patients⁽¹⁹⁾.

3. Nervous effects

3.1. Local anesthetic effect

A solutions of trans-anethole administered into the rabbit conjunctival sac increased the number of stimuli required to evoke the conjunctival reflex ($p < 0.01$) comparable to the effect of procaine. Trans-anethole reduced the electrically-evoked contractions of rat phrenic nerve-hemidiaphragm by 10.3% at 1 pg/ml, by 43.9% at 10 pg/ml, by 79.7% at 100 pg/ml and by 100% at 1000 pg/ml⁽⁴⁸⁾.

3.2. Anticonvulsant effect

The anticonvulsant and anti-hypoxia effects of anise oil were tested in seizure induced by pentylenetetrazol (PTZ) injection and neuronal hypoxia induced by oxygen withdrawal as well as on production of dark neurons and induction of long-term potentiation (LTP) in *in vivo* and *in vitro* experimental models of rat brain. Anise oil significantly prolonged the latency of seizure attacks and reduced the amplitude and duration of epileptiform burst discharges induced by intraperitoneal injection of PTZ. It also significantly inhibited production of dark neurons in different regions of the brain in epileptic rats. Furthermore, it significantly enhanced the duration of the appearance of anoxic terminal negativity induced by oxygen withdrawal and inhibited induction of LTP in hippocampal slices⁽⁴⁹⁾.

The antiepileptic effect of percolated extract of *Pimpinella anisum* was investigated in picrotoxin induced seizure in mice. The extract increased the delay in the onset of seizure in the mice. The most effective dose of extract was 200mg/kg ($p < 0.05$). In addition, this dose delayed the time of death in mice ($p < 0.01$). The effect of the extract with a dose of 200 mg/kg was more satisfactory than phenobarbital (40mg/kg) on delaying death time⁽⁵⁰⁾.

The essential oil suppressed tonic convulsions induced by pentylenetetrazole or maximal electroshock in male mice. It also elevated the threshold of PTZ - induced clonic convulsions in mice⁽⁵¹⁾.

The effects of fruit essential oil of anise on the bioelectrical activity of snail neurons were studied in control condition or after PTZ- induced epileptic activity. The oil changed the firing pattern from regular tonic discharge to irregular and then to bursting in intact cells or resulted in the robustness of the burst firing and the steepness of the paroxysmal shift

induced by PTZ treatment. It also significantly increased the firing frequency and decreased both the after-hyperpolarization potential following single action potential and the post-pulse after-hyperpolarization potential ⁽⁵²⁾.

3.3. Hypnotic effect

Intaperitoneal administration of essential oil at 50 mg/kg or trans-anethole increased the pentobarbital-induced sleeping time of mice by 93.5% ($p < 0.01$) ⁽⁵³⁾.

3.4. Antidepressant effect

The antidepressant-like effect of aqueous and ethanolic extracts (50, 100 and 200 mg/kg, ip) of *Pimpinella anisum* fruit was investigated in mice by using forced swimming test (FST) and tail suspension test (TST). All the three doses of aqueous and ethanolic extracts (except 50 mg/kg of aqueous extract in FST) significantly and dose-dependently reduced the immobility times in both FST and TST. All doses of extracts increased the swimming time dose-dependently, without any significant change in climbing time ⁽⁵⁴⁾.

3.5. Anxiolytic effect

The effects of the aqueous extract of *Pimpinella anisum* seeds on exploratory activity and emotional behavior in rats was studied using the open field and elevated plus maze tests. In open field test, only rearing was reduced in the extract at a dose of 0.5 g/kg. At a dose of 1.0 g/kg, only the initiation of exploratory activity was delayed, without impairing the rats general activity. A dose of 2.0 g/kg induced a reduction in the rats habituation during the open field test within the same session, as evidenced by the maintenance of high levels of peripheral locomotion and rearing throughout the test. On the elevated plus maze test, no alterations were observed in the responses of the rats ⁽⁵⁵⁾.

3.6. Anti-cholinesterase activity

Ethanolic extract from the fruits of *Pimpinella anisoides*, showed anti- AChE and anti- BChE activity, with IC₅₀ values of 227.5 and 362.1 microg/ml, respectively. The abundant constituents of the extract (trans-anethole) exhibited the highest activity against AChE and BChE with IC₅₀ values of 134.7 and 209.6 microg/ml, respectively ⁽⁵⁶⁾.

3.7. Neuroprotective effect

The effect of *Pimpinella anisum* aqueous extract against lead acetate (Pb) neurotoxicity was studied in rats. Pregnant rats received 0.2% of Pb in drinking water, and treated with the aqueous extract after weaning with dose of 750 mg/kg and for 15 successive days. Lead induced a hyperactivity in the open field which was reduced after administration of the extract. In the forced swimming test, the extract enhanced significantly the mobility time compared with intoxicated group. The time spent in the dark compartments in dark and light test was reduced after treatment with the extract orally. Lead caused significant increase in lactate dehydrogenase, lipid peroxidation and alkaline phosphatase, these biochemical changes were ameliorated by the extract ⁽⁵⁷⁾.

3.8. Immunomodulatory effect

The effects of anise decoction consumption on lymphocytes activity, and nitric oxide (NO) production were studied in mice after 1 and 2 weeks treatment. Lymphocytes activity of anise treated mice was significantly more than that in control group at week 2. The spleen cells showed a significant higher lymphocyte proliferative response to *in vitro* challenge with phytohaemagglutinin at the second week of treatment. The increase in mouse foot thickness as indicator of delayed type of hypersensitivity was less in anise treated mice compared to control group. Nitric oxide production by peritoneal macrophages in response to activation with lipopolysaccharides was decreased by anise treatment after 1 and 2 weeks of treatment and no significant changes in CD4 and CD8 were noticed either at week 1 or 2 of treatment ⁽⁵⁸⁾.

3.9. Anticancer effect

The cytotoxicity silver nanoparticles (AgNPs) using an aqueous extract of *Pimpinella anisum* seeds was investigated in colon cancer cells (HT115). Among the different tested concentrations of nanoparticles, doses $< 10 \mu\text{g}$ showed few adverse effects on cell proliferation without variations in viability, whereas doses $> 10 \mu\text{g}$ led to increased cytotoxicity ⁽⁴²⁾.

The cytotoxic effect of methanolic and ethanolic extracts and essential oil of *Pimpinella anisum* was investigated against gastric cancer cell line (AGS) and angiogenesis of HUVEC cells. The ethanolic extract inhibited cell proliferation of the AGS cells in $30 \mu\text{g/ml}$ at 48 hours after treatment but it had no significant effect on fibroblast cells. The inhibitory effect

of methanolic extract was much better than the ethanolic extract at the same concentrations. The essential oil of the plant had the highest inhibitory effect on cancer cells compared with the alcoholic extracts. The extracts and essential oil possessed inhibitory effects on the angiogenesis in HUVEC cells ⁽⁵⁹⁾.

The ethanolic extract of *Pimpinella anisum* seed possessed cytotoxic effect against human prostate cancer cell line (PC-3) at concentrations safe to normal cells [rat skeletal muscle cell line (L6)]. The seeds extract exerted anti proliferative and apoptotic effects, with IC₅₀ of 400 µg/ml to cancer cells ⁽⁶⁰⁾.

Pimpinella anisum seed extract possessed significant cytotoxic effect on KB cell line at 0.0052 mg/ml ⁽⁶¹⁾.

3.10. Effect on milk production

The effect of aqueous and ethanolic extracts of the seeds on milk production in rats was evaluated by measuring the pups' weights during the suckling period. The aqueous (1 g/kg) and ethanolic extracts (1 g/kg) increased the milk production significantly ($p < 0.001$), with about 68.1% and 81% more milk being produced, respectively. The pups gained weight during the study period with the aqueous (0.5 and 1 g/kg, $p < 0.05$) and ethanolic (0.5 and 1 g/kg, $p < 0.01$) extracts ⁽⁶²⁾.

3.11. Effect on smooth muscles

Three ethanol: water extracts (40:60, 60:40 and 80:20) of *Pimpinella anisum* aerial parts were tested for activity in the rat anococcygeus smooth muscle. The three extracts inhibited acetylcholine- induced contraction. The effects elicited by the extracts of *Pimpinella anisum* involved the participation of NO and subsequent activation of the NO-cGMP pathway ⁽⁶³⁾.

Aniseed essential oil (200 mg/l) produced a complete relaxation of carbachol- induced contractions in isolated tracheal smooth muscle of Guinea pig. While, it increased the contraction force in electrically-stimulated Guinea pig ileal smooth muscle ⁽⁶⁴⁾.

The bronchodilatory effects of aqueous and ethanol extracts and essential oil were studied in precontracted isolated tracheal chains of the Guinea pig. Aqueous and ethanol extracts, essential oil showed significant relaxant effects. The bronchodilatory effects of essential oil, aqueous, and ethanol extracts of *Pimpinella anisum* was not due to an inhibitory effect of histamine (H1 receptor) or stimulatory effect of β_2 - adrenergic receptors, but due to inhibitory effects on muscarinic receptors. Furthermore, a potassium channel opening effect for this plant, contributed on its relaxant effect on tracheal chains of Guinea pig ⁽⁶⁵⁻⁶⁶⁾.

The modulating effect of *Pimpinella anisum* extract in term-pregnant rat uterine contractility was investigated in addition to studying of the possible mechanisms. Application of the extract significantly reduced uterine contractions generated spontaneously or induced with oxytocin, Bay K8644, and carbachol in a concentration-dependent manner. In depolarized myometrium, the extract significantly reduced the tonic force induced by high-KCl solution. It also prevented oxytocin-induced transient contraction in the entire absence of external calcium ⁽⁶⁷⁾.

3.12. Dermatological effect

Extracts which contain high farnesyloxy coumarin were assayed as modulators of melanogenesis in cultured murine Melan A cells. A parallelism between the content of the coumarin and the depigmenting effect was recorded at a dose of 100 µg/ml ⁽⁶⁸⁾.

3.13. Laxative effect

A phytotherapeutic tea containing *Pimpinella anisum*, *Foeniculum vulgare*, *Sambucus nigra* and *Cassia augustifolia* was evaluated for its laxative in a randomized clinical trial. The colonic transit time, measured radiologically was 15.7 hours in the active treatment period and 42.3 hours in the placebo treatment ($p < 0.001$). Number of evacuations per day increased during the use of active tea. Patient perception of bowel function was improved ($p < 0.01$), but quality of life did not show significant differences among the study periods. No significant differences were observed in terms of adverse effects throughout the study period ⁽⁶⁹⁾.

3.14. Prevention of osteoporosis

The ability of *Pimpinella anisum* extract to stimulate the differentiation and mineralization of osteoblastic cell culture, to induce, like antiestrogens, the insulin growth factor binding protein 3 (IGFBP3) in MCF-7 breast cancer cells, and to

proliferate cervical adenocarcinoma (HeLa) cells were investigated. The extract at a concentration range 10-100 microg/ml stimulated osteoblastic cell differentiation and exhibit antiestrogenic effect on breast cancer cells without proliferative effects on cervical adenocarcinoma cells. The presence of estradiol inhibited the antiestrogenic effect induced by the extract on MCF-7 cells, suggesting an estrogen receptor-related mechanism⁽⁷⁰⁾.

3.15. Effect on premenstrual syndrome

The effect *Pimpinella anisum* on the intensity of the symptoms of premenstrual syndrome (PMS) was investigated in a randomized double-blind controlled clinical trial with the using of premenstrual symptoms screening tool (PSST). Participants in the intervention group received 110 mg capsules of anise three times day, and the control group received similar capsules contained starch. Treatment started 7 days before the start of the menstruation and continued until 3 days after. Anise was effective in decreasing the symptoms of premenstrual syndrome in comparison to placebo⁽⁷¹⁾.

3.16. Toxicity and side effects

The aqueous and ethanolic extracts of *Pimpinella anisum* seeds caused no mortality when used orally in mice after 24 and 48 hours of treatment in dose range from 0.5 to 32 g/kg. The intraperitoneal LD₅₀ of the aqueous and ethanolic extracts were 4.93 and 3.77 g/kg, respectively, and the maximum safe dose was 2.2 g/kg⁽⁶²⁾.

Anise seeds 2 g twice daily in a form of anise tea for 4 weeks in healthy volunteers didn't significantly change complete blood count, lipid profile, liver function tests, kidney function tests, testosterone, and blood pressure, but it significantly decreased fasting blood sugar and lymphocyte % and significantly increased neutrophils %⁽⁶⁴⁾.

Rare cases of contact dermatitis to anethole containing preparations were recorded ⁽⁷³⁻⁷⁴⁾. Furocoumarins in anise can cause photosensitivity reactions ⁽⁷⁵⁾

4. Conclusion

This review discuss the chemical constituent, pharmacological and therapeutic effects of *Pimpinella anisum* as promising herbal drug because of its safety and effectiveness.

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