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FENNEL AND ANISE AS ESTROGENIC AGENTS*

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Summary

Fennel, *Foeniculum vulgare*, and anise, *Pimpinella anisum*, are plants which have been used as estrogenic agents for millennia. Specifically, they have been reputed to increase milk secretion, promote menstruation, facilitate birth, alleviate the symptoms of the male climacteric, and increase libido. In the 1930s, some interest was shown in these plants in the development of synthetic estrogens. The main constituent of the essential oils of fennel and anise, anethole, has been considered to be the active estrogenic agent. However, further research suggests that the actual pharmacologically active agents are polymers of anethole, such as dianethole and photoanethole.

Fennel, *Foeniculum vulgare* Mill., and Anise, *Pimpinella anisum* L., are well-known Umbelliferous plants which produce small, oblong fruit commonly called "seeds". Many people have encountered these "seeds", or their essential oils, as flavoring agents in food.

For example, anise seeds are sprinkled on top of certain Italian cookies, and the essential oils of either anise or fennel impart the characteristic flavor to liquorice candy. Both plants have been used as ingredients in alcoholic beverages; fennel has been used as a gin botanical and in the manufacture of the Greek drink *Ouzo*.

Both plants also have a long history of medicinal use. Today, the medical practitioner prescribes estrogens for a variety of conditions which are generally correlated with deficiencies in the naturally produced sex hormones. For example, women with menstrual irregularities or delayed menstruation may be given synthetic estrogens. Menopausal women commonly receive estrogens to help allay the hot flushes, nausea, and other symptoms of this decrease in the body's natural hormonal level. It is of interest to note that the symptoms of the male counterpart, the male climacteric, often respond favorably to estrogen therapy (Ganong, 1975; Greenblatt, 1965; Guyton, 1976; Goodman and Gilman, 1975).

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Synthetic estrogens are used in the farmyard as well as in the hospital. Some dairymen use estrogens to increase the yield of milk from their stock (Folley and Malpress, 1944 a, b; Frazier and Mu, 1935; Hammond and Day, 1944). Many studies also note that cattle given estrogens mate more readily, and, by and large, administration of estrogens to experimental animals has been found to increase libido.

Most physicians and laymen alike consider estrogen therapy a new development in the history of medicine. While it is true that chemists did not synthesize estrogens until the late 1930s, it is also true that healers have prescribed estrogenic substances for thousands of years.

How humankind first learned of the effects of plants such as fennel and anise remains to be seen; however, it is possible that herdsmen were the first to discover the estrogenic activity contained in them. It has been noted that when milking cows or goats fed on these plants, milk production increases, and the taste of the plants can be found in the milk (de Bairacli, 1973). As people learned to follow the herds, and take the milk, they may also have first learned of the effects of different plants on milk production.

Whatever the circumstances surrounding the discovery of the estrogenic effects of fennel and anise actually were, it is a fact that human beings have used these plants for millennia. In the first century A.D. Dioscorides notes, "Fennel herb itself is of the force to draw down milk, as doth the seed being drunk" and, "it expels the menstrua" (Gunther, 1968, p. 314). Of anise, he writes that it too "draws down the milk" (Gunther, 1968, p. 299).

Pliny, in his *Natural History*, describes effects of anise which would appear to rely on its estrogenic properties:

> Dalion the herbalist prescribed a poultice of anise and parsley for women in labour, and also for pain in the womb; he recommended it be taken with dill in drink for women in labour. (Pliny, Loeb edn., Vol. VI, p. 111.)

He comments further:

> Pythagoras says that to smell it makes for easier childbirth, and that immediately after delivery it should be given in a draught with a sprinkling of pearl barley. (Pliny, Vol. VI, p. 111.)

Pliny's final word on anise is, "It is aphrodisiac" (Pliny, Vol. VI, p. 113).

Two thirteenth century herbals detail the estrogenic activity of fennel and anise. Rufinus, in his Herbal, notes that both plants encourage milk production and stimulate venery (Thorndike, pp. 361 and 389). In the herbal *Macer Floridus de Viribis Herbarum*, once the standard herbal of Europe, the authors write: "The nurse that has want of or desires milk shall eat often or drink fennel or the juice, so she shall have milk enough." (Frisk, 1949, p. 88.) Anise is also said to increase the flow of milk (Frisk, 1949, p. 105). It is also asserted that "Fennel seed drunk with wine stirreth lechery." (Frisk, 1949, p. 89.) In addition, fennel's reputed effect on the male climacteric is discussed:

> The decoction of fennel drank often will make old men to seem long young. This proveth authors and philosophers, for serpents, when they be young and woolly, wax strong, mighty and young once more, they go and eat often fennel, and so become youthful and mighty. (Frisk, 1949, pp. 89 - 90.)

The use of fennel by serpents is discussed by a number of authors, many who note that snakes casting off their skins eat fennel to restore their eyesight (Pliny, 1942, Vol. III, pp. 71 - 73).

A story which may be related to this is told by Aelian in his *On the Characteristics of Animals*:

> It is said that Prometheus stole fire, and the story goes that Zeus was angered and bestowed upon those who laid information of the theft a drug to ward off old age. So they took it, and placed it upon an ass. The ass proceeded with the load on its back; and it was summer time, and the ass came thirsting to a spring in its need for a drink. Now the snake which was guarding the spring tried to prevent it and force it back, and the ass in torment gave it as the price of the loving-cup the drug that it happened to be carrying. And so there was an exchange of gifts; the ass got its drink and the snake sloughed off his old age, receiving in addition, so the story goes, the ass's thirst. (Aelian, 1959, p. 73.)

While Aelian does not identify this drug as fennel, it seems likely that this is what the ass carried on its back, for it is well-known that fennel plays a central role in the myth of Prometheus, who hid the fire he stole from the gods in a hollow fennel stalk (Aeschylus, 1942; Hesiod, 1959). In Aeschylus' version, fennel is referred to as a magical drug capable of producing immortality. This immortality may have involved more than the increase in a person's productive sexual life by substituting a plant chemical for the deficient sex hormones. Psychoactive and psychedelic effects of fennel and anise, and the primary chemical constituent, anethole, have been noted. Throughout the ages, users of psychedelic substances have reported undergoing *experiential* immortality, and this may be what Aeschylus had in mind when he tells us that the coming of the sacred fennel caused mortals to "cease foreseeing doom".

These psychoactive effects may also play a significant role in the aphrodisiac qualities noted in the literature. The 17th century herbal of Gerard (1633) notes that "anise maketh aboundance (*sic*) of milk", and "stirreth up bodily lust". Likewise, Culpepper notes that "The leaves or seed [of fennel] boiled in barley milk and drunk, are food for nurses to increase their milk."

In the United States, the employment of fennel as an estrogenic agent persisted into the 20th century. *The National Standard Dispensatory* of 1916 describes how an infusion of fennel "is occasionally given to increase the lacteal secretion, and to establish the menstrual flow." (Hare *et al.*, 1916, p. 63.) Essential oil of fennel is likewise described as "thought to possess emmenagogue and galactagogue properties." (Hare *et al.*, 1916, p. 1129.)

It is of interest to note that fennel and anise were not overlooked in the development of modern synthetic estrogenic agents. Among the scientists who investigated the effects of fennel constituents was Sir Charles Dodds, who developed the first humanly synthesized, orally effective estrogen in 1938 (Dodds *et al.*, 1938). At this time, the estrogenic activity of fennel oil and anethole were demonstrated by Zondek and Bergmann (1938). In subsequent studies by a number of researchers, the estrogenic activity of anol, or demethylated anethole, is clearly shown. It is reported that anol causes growth of the lobule-alveolar system in the mammary glands of immature

female rabbits (Gomez and Turner, 1939) and induced estrucs in mice and other experimental animals (Dodds and Lawson, 1937a; Gomez and Turner, 1938; Lewis and Turner, 1941; Supniewski and Hano, 1937). Anol also gave positive results in the Jadassohn nipple test, a test which involves the measurement of changes induced in the nipples of guinea pigs subjected to the cutaneous application of sex hormones (Jadassohn, 1938).

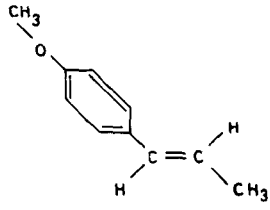
As it turned out, anol itself was eventually found to be inactive, and it was shown that only polymers of anol possess activity (Preobrazhenskii *et al.*, 1944, Campbell *et al.*, 1938; Dodds and Lawson, 1937b; Dansi *et al.*, 1937; Madaeva *et al.*, 1953; Maksimov *et al.*, 1951). These compounds were actively considered as therapeutic agents; however, in time, other chemicals superceded them. In the light of these studies, one may legitimately ask: Is the estrogenic activity of fennel and anise also due to polymerized anethole, rather than to anethole itself? In the study of Zondek and Bergmann, cited above, fennel oil was found to be five times more active than putative "pure" anethole. If polyanethole compounds are, in fact, the active components in anise and fennel, one could explain the greater activity of fennel oil over "pure" anethole as due to the former's higher concentration of polymerized anethole. Along with this, the activity of so-called pure anethole could be postulated to be due to contamination with polymers of anethole. In support of this suggestion, one study shows dianethole as exhibiting pronounced estrogenic activity (Campbell *et al.*, 1938). It might prove interesting to perform these experiments again using carefully purified and analyzed chemicals.

The structure of anethole

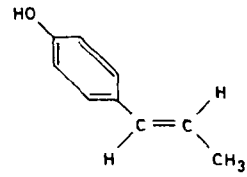
Anethole, or *p*-propenylmethoxy benzene, is a benzene ring with a single methoxy group *para* to the double-bonded propenyl group. Like a number of similar compounds in plants, anethole bears a striking resemblance to the catecholamines epinephrine, norepinephrine, and dopamine. This structural similarity appears to be responsible for the various sympathomimetic effects fennel and anise have been thought to exert on the organism; like ephedrine, these plants are described as bronchodilators, and, like amphetamine, fennel is said to facilitate weight loss (Frisk, 1949, and elsewhere).

Whether or not this resemblance to the catecholamines has any bearing on the estrogenic activity remains to be shown. It is worth noting that recent studies indicate that dopamine acts to inhibit the secretion of the milk-producing hormone prolactin (Agnati, 1977; Macleod and Login, 1977; Mietes, 1977). In the light of this finding, one plausible means by which anethole might influence milk secretion would be by competing with dopamine at the appropriate receptor sites, thereby inhibiting the inhibition by dopamine of prolactin secretion.

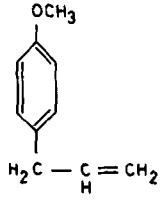
Anethole is related to a number of psychoactive chemicals such as mescaline and asarone, found in the rhizomes of *Acorus calamus*, and myristicin found in nutmeg. It is also closely related to dillapiol, found in Indian dill,



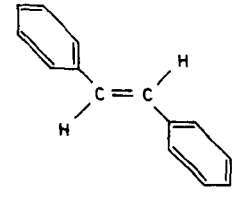
Anethole, 1-Methoxy-4-(1-propenyl)benzene



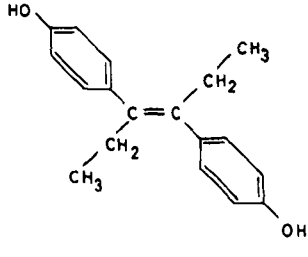
p-Anol, 4-(1-Propenyl)phenol



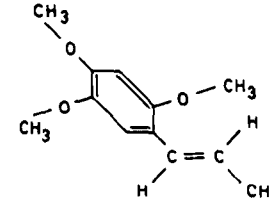
Estragole, Chavicol Methyl Ether, 1-Methoxy-4-(2-propenyl)benzene



trans-Stilbene, 1,1'-(1,2-Ethenediyl) bis [benzene]



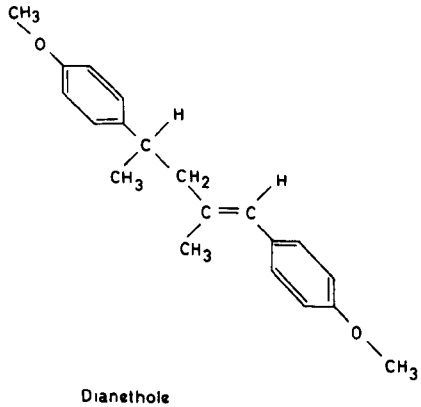
Diethylstilbestrol, (E)-4,4'-(1,2-Diethyl-1,2-ethenediyl)bisphenol



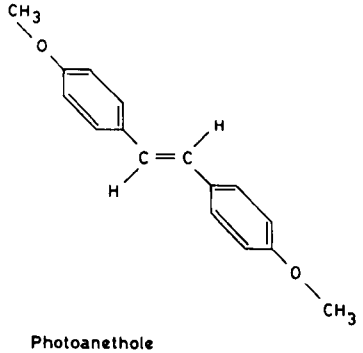
Asarone, (E)-1,2,5-Trimethoxy-4-(1-propenyl)benzene

which may interbreed with fennel. Dill has also been said to increase milk secretion (Gerrard, 1633, p. 1033; Gunther, 1968, p. 301.)

It is no surprise that the estrogenic agents stilbene, diethylstilbestrol, and related compounds also resemble polymerized anethole, since it appears that these chemicals were originally modelled after the polymers dianethole and photoanethole. The estrogenic activity of photoanethole was briefly investigated in poultry; however, its relative weakness caused interest to move to other agents (Jaap, 1945).



Dianethole



Photoanethole

Toxicity of fennel and anethole

In a recent study the acute oral LD_{50} for anethole in rats was found to be 2090 mg/kg. (By way of comparison, the acute oral LD_{50} for vanillin was 1580 mg/kg.) In this study, anethole was found to be less toxic than its allyl analog, estragole, a major constituent of tarragon oil. Repeated doses of one-third the LD_{50} of anethole given to rats (695 mg/kg) caused "mild liver lesions, consisting of slight discoloration, mottling, and blunting of the lobe edges." On a scale of 0 to 4 (0 = normal liver, 4 = severe liver damage) the effect of anethole on the liver was rated at 0.5 (Taylor, 1964). It would therefore appear that in normal therapeutic dosages anethole would have minimal hepatoxicity. When anethole was fed to rats daily for one year as 0.25% of the diet, no hepatic damage was seen (Taylor, 1964).

Another recent study reports the acute oral LD_{50} of fennel oil, using rats, as 3.8 mg/kg (Opdyke, 1974). Fennel oil has been approved for food use by the F.D.A., and was granted GRAS status by the F.E.M.A. (1965) (Opdyke, 1974). The Council of Europe (1970) included fennel oil in the list of fruits and vegetables for which no restrictions were proposed (Opdyke, 1974).

Fennel oil was officially included in the *United States Pharmacopeia* for many years; more recently it appeared as a flavoring agent. However, at present, it is no longer official. As of 1977, it was included in the pharmacopeias of a number of countries, including Argentina, Austria, Brazil, Chile, China, Czechoslovakia, Germany, Hungary, India, Japan, Jugoslavia, The Netherlands, Poland, Roumania, and Switzerland (Ainley, 1977).

In the light of the long historical usage of fennel and anise as estrogenic agents and their documented low toxicity and lack of demonstrable carcinogenicity, the re-introduction of these plant drugs into modern medical usage may be warranted. As recently noted, traditional medicine is the only mode

of health care delivery for 75% of the world's population, and plants are the primary therapeutic agents in traditional medicine (Marini-Bettòlo, 1979). Hence, the integration of fennel and anise into the medical practices in developing nations, and, for that matter, industrial nations, may have merit. Unlike most synthetic estrogens, these plants are inexpensive, easily cultivated, non-carcinogenic, and yet gentle and efficacious in their effect. They would be of use in a number of medical situations. Furthermore, the extraction of the essential oils requires nothing more than basic technology and could be carried on anywhere in the world.

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