Cultivation of Fennel in Washington

*By Troy E. Becker, Edwin J. Isler and Forest J. Goodrich**

Because of the economic and pharmaceutical importance of the fruit and volatile oil of *Fœniculum vulgare*, Miller, and since they are largely imported into the United States, cultivation of the plant has been conducted for several years in the College of Pharmacy drug garden. The character and quality of the products have been determined and comparisons made with the imported fruit and official oil. It is interesting to note that fennel has been cultivated for the past ten centuries in the old world. Plants have been grown in this country but not in sufficient quantities to meet the demand for the fruit and volatile oil.

EXPERIMENTAL

Description of Plant.—Large perennial herb attaining a height of five and one half to six feet. The stem is furrowed, glaucous, green and branched. Leaves are alternate, twice pinnate with narrow pinnea. The root stock is thick, the flowers a pale yellow and arranged in a compound umbel. The fruit is a large cremocarp. All parts of the plant are aromatic.

Planting and Collection of Fruit.—The soil was a good sandy loam with considerable limestone. The plantings were made in March in rows eighteen inches apart. The plants were later thinned to about twelve inches apart in the rows. No fruit was obtained from the first year's planting. The latter part of September of the third year, the fruiting branches were cut off and the ripe fruit threshed, screened and allowed to dry. The yield of air-dried fruit was slightly under two tons per acre, 3960 pounds.

Extraction Ash and Oil.—Several pounds of the fruit were ground to approximately a number forty powder and reserved for experimental use.

Successive extractions of forty gram samples gave the following percentage extractions:

Solvent	Extractive
Petroleum ether	19.62
Ethyl ether	2.31
Chloroform	2.29
Ethyl acetate	3.01
Ethyl alcohol	4.70

Two-gram samples of the powdered fruit were ignited to constant weight and the following determinations made:

Total ash	7.14
Water insoluble ash	4.32
Acid insoluble ash	0.60

Several pounds of the ground fruit were macerated and steam distilled until all of the oil was carried over. The following results were obtained:

Yield of Volatile Oil	4.1%
Properties of Oil	
Sp. gr. at 25° C.	0.9641
Soluble, 10 parts 80% alcohol	
Not entirely sol., 1 part 90% alcohol	
Optical rotation	−14.1°
Refractive index 20°	1.534
Odor, strongly fennel-like, somewhat pungent	
Color, pale yellow	
Congealing point	2.9° C.
Heavy metals test	negative
Appearance, bright	
To litmus, slightly acid	
U. S. P. Requirements for Oil of Fennel	
Sp. gr.	0.953/0.973
Solubility	8/80%
Solubility	1/90%
Optical rotation	−12°/24°
Refractive Index 20°	1.5280/1.5380
Odor, fennel-like	
Color, pale yellow	
Congealing point	3° C. or above
Heavy metals test	negative (approx.)

The solubility in alcohol and the congealing point is slightly below U. S. P. requirement, otherwise, the oil meets the requirements of the U. S. P. XI by all constants and tests.

Histological sections were made of the fruit and comparisons made with species grown in Europe. The Washington-grown fruits are somewhat lighter in weight and not as full and plump as some European samples examined. The Vittæ in many cases seem to be somewhat more ellipsoidal.

Considering the large yield of American-grown fennel and the fair quality of oil, it would seem worth while to develop *Fœniculum vulgare* cultivation in this country, at least in this section of the country where growing properties have been established.

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A Permanently Stable Elixir of Ferrous Sulfate*

By Donald A. Clarke†

It is the purpose of this report, not to disclose any startling discoveries, for such have not been made, but merely to recount a simple study which has been conducted on the preparation of an elixir of ferrous sulfate

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so that other individuals who might be faced with a similar problem may find a resolution in the products of our efforts.

Through the medium of the Formulary Committee of The New York Hospital, we were requested to supply various clinical services of the hospital with a liquid preparation of ferrous sulfate which would lend itself readily to the administration of ferrous sulfate to children, or for which dosage schedules, when necessary, could be made more flexible than tablets of the salt would allow.

Due to the fact that the required dose of any particular iron preparation to be used for the treatment of iron deficiency is proportionately smaller for infants and children than the dose for adults, a liquid preparation of a good iron salt is needed for treating the range of patients from newborns to adults to allow flexibility in administration. Also, it is often impossible to administer a tablet containing a definite quantity of such a salt to infants and children either because of incapability of swallowing such a tablet or, due to preconditioning, outright refusal to take a tablet. The latter circumstance is also found true in the case of some adults. These preconditioned cases, however, will often take a good appearing, well flavored, liquid preparation. Such a preparation of a ferrous salt must be permanent indefinitely and must retain its original appearance indefinitely under all practical conditions of use. No dissertation is necessary to point out the obviousness of these two fundamental requirements.

The development of a formula and a technique for such a preparation of ferrous sulfate was almost entirely one of "feeling in the dark." We were convinced that any available proprietary preparation was not satisfactory from the standpoint of our requirements because rapid decomposition and precipitation of what appears to be ferric hydroxide occurs when exposed to air (repeated openings of the bottle) or direct sunlight. A formula reported by Mackay and Jacob (5), which they stated would give a preparation which would remain stable for about sixty days, gave us, at the most, six to seven days stability. Various antioxidants were used by these authors to retain the ferrous iron in that state. Other than this one report, we could find nothing in the literature of apparent value. We, therefore, proceeded on a trial and error basis.

We found it helpful in approaching the problem to first exhaust all simple and usually well-known possibilities. In this instance our answer apparently lay in the use of one of the simplest agents available. Knowing that a small amount of sugar will usually protect the ferrous ion from oxidation for a short period of time in certain preparations of ferrous salts, we theorized that the amount of oxidation of ferrous sulfate in solution over a period of time should be inversely porportional to the concentration of sugar present in the same solution and, likewise, the length of the period of protection should be directly porportional to the amount of sugar present. On the basis of this theory, we felt that there must be a point where a concentration of sugar would be adequate to protect completely and indefinitely a given quantity of ferrous sulfate from oxidation into a ferric state.

EXPERIMENTAL

It was requested that this liquid preparation of ferrous sulfate have a strength of 0.1 Gm. of the salt per 4 cc. Using 4.6 Gm. of U. S. P. XI Ferrous Sulfate per 100 cc. (based on the U. S. P. XI minimum content of 54.36% $FeSO_4$, this is equivalent to 0.1 Gm. of Exsiccated Ferrous Sulfate per 4 cc.) we found that after 24 hours of normal laboratory conditions (no direct sunlight) the amount of ferric ion present was roughly proportionally smaller in samples containing increasingly larger percentages of sugar; *i. e.*, 10%, 20%, 30%, 40%, 50%, 60%, 70% and 80%. This rough comparison was established using an 80% sugar concentration as standard and precipitating the ferric ion present with potassium ferrocyanide test solution. Later, a series was studied using potassium thiocyanate 3*N* solution as a reagent for producing a characteristic color in the presence of the ferric ion. All preparations were compared against a standard solution containing a known quantity of ferric iron by an electrocolorimeter. The results of this study, when plotted, substantiated our theory. The curve plotted out slightly above the concentration of a saturated solution of sugar in water, *i. e.*, 85%; however, we are inclined to believe that the ferric iron present in an 85% sugar preparation is almost entirely ferric iron occurring in the salt before in-

corporation. Nevertheless, we concluded that our optimum preparation should be one using simple syrup as the solvent. Following the curve in such a preparation, it was felt we might rightfully expect either the presence or formation of some ferric iron to be indicated. How long before this formation of ferric iron would become apparent to the eye could only be determined by trial. We found that by adding a sufficient quantity of simple syrup (definitely saturated) to the required amount of ferrous sulfate to make a given quantity of preparation and then triturating in a mortar to grind the crystals, the salt would dissolve readily. For large quantities, the weighed salt was ground into tiny particles under a small quantity of simple syrup, the mixture transferred to a graduated glass-lined vat and sufficient simple syrup used in rinsing the mortar to make the desired volume. Solution was effected by agitation with a mechanical stirrer.

Spirit of Peppermint was used to flavor this preparation for three main reasons. By consensus of opinion, the flavor of peppermint is accepted to be the most popular among all peoples, and especially among children. The menthol contained in peppermint has a slight anesthetizing effect on the taste buds of the tongue. In the concentration used it was found to completely cover the disagreeable ferrous taste inherent in a similar preparation without flavoring. And, finally, it can be stated that the designation "elixir" might be open to question because this preparation does not necessarily conform to such terminology. Because the title, elixir, has been popularized commercially for this type of liquid ferrous sulfate preparation, we were faced with the necessity of making a preparation which could be dispensed when an "elixir" was prescribed or of changing the conventional terminology in the minds of some five hundred staff physicians who might prescribe this medicament at The New York Hospital. Because of the desire to assure the use of our preparation, we, therefore, added a slight amount of alcohol in the form of Spirit of Peppermint to make this liquid one which could at least be described theoretically as being hydroalcoholic and fit the designation, "elixir."

The observable stability of this preparation was found to be a period of three to four weeks, at the end of which time slight precipitation of ferric hydroxide was apparent, especially if the control container had been opened several times or was at all exposed to direct sunlight. As noted previously, we believe this is due to the presence of the ferric ion in the ferrous salt when purchased. It was therefore decided to increase slightly the acidity of the preparation by use of a small amount of citric acid. Upon the addition of 0.2% citric acid, our objective was achieved. The original control bottles, taken from the first lot treated, are now nearly ten months old, have been subjected to every conceivable condition of storage, including prolonged exposure to air and direct sunlight and exposure to high and low temperatures. The samples thus treated retained the same appearance in every respect as control samples stored under optimum conditions, the latter being of the same appearance at the time of this writing as originally. This preparation, the formula for which follows, can therefore be considered permanent for all practical purposes.

Elixir of Ferrous Sulfate

Ferrous Sulfate, U. S. P. XI	4.6 Gm.
Citric Acid	0.2 Gm.
Spirit of Peppermint	0.2 cc.
Simple Syrup, U. S. P. XI. *q. s.*	100.0 cc.

CLINICAL EVALUATION

Clinically, the preparation has proved effective. The Department of Pediatrics of The New York Hospital has studied the effectiveness on iron deficient children who had received no therapy previous to admission. Adequate response was noted in from three to four weeks as determined by the increase in hemoglobin content of the blood.

COMMENTS

It is pertinent to note that the more fresh the supply of ferrous sulfate, the less the amount of the ferric ion present. No crystal of ferrous sulfate is free from ferric ions unless it has been prepared and stored under an atmosphere devoid of all oxygen or oxidizing agents.

A peculiar phenomenon occurs in the elixir made from relatively old samples of the salt. When made from a fresh salt, the elixir is almost colorless, except for a very slight bluish, fluorescent-like color which can be seen through transverse light. Elixirs made from older samples of the salt develop a light green color about an hour after manufacture, which becomes increasingly noticeable the older the sample of salt used. This color is apparently due to the presence of citric acid. When an elixir, which has developed this light green color, is subjected to actinic light, the color almost immediately disappears, but when removed from exposure, it regains its color within a short time. It is important to note at this point that any green color which develops in preparations made according to the formula given above does not increase in intensity after prolonged exposure to light, nor does the original amount of ferric ion increase so that a change can be detected colorimetrically as described earlier.

After this study had been completed and the elixir was undergoing clinical evaluation, various and sundry iron preparations of this type made by private formulas were brought to our attention. We examined a number of these preparations from a comparative standpoint. One such preparation makes use of the principle for stabilizing ferrous salts which we found satisfactory. The formula for this preparation calls for Ferrous Sulfate 3.5 Gm., Alcohol 12 cc., Citric Acid *q. s.* for solubility and Distilled Water *q. s.* to make 100 cc.

In preparing samples of this preparation for examination, we used the same quantity of citric acid employed in our preparation, *i. e.*, 0.2%. The finished preparation remained practically colorless for about one hour after manufacture, at which time a pronounced green color began to develop. The appearance of the green color, which became progressively intense, was taken as evidence of an increasing amount of ferric iron in the preparation. The preparation, examined colorimetrically at intervals revealed that the amount of ferric iron increased until precipitation occurred. When exposed to ordinary daylight with about two hours of direct sunlight per day on intermittent days when the sun shone, the preparation became colorless after a short time. With the passing of daylight, the green color recurred with greater intensity than was the case before the period of exposure. This continued until after an average of about eighteen days when the preparation turned purple, appeared colloidal upon examination, and gave the tyndal cone effect with transverse light. Twenty-four hours later a precipitate of what appeared to be ferric hydroxide began to form and continued until a large portion of the iron salt was precipitated.

Other preparations examined behaved in similar manner. All showed decomposition after varying periods of exposure to actinic light, air, cold or heat, a combination of the four agents or any two or three of them.

CONCLUSIONS

Using a simple approach, we have developed a formula for an elixir of ferrous sulfate which appears to us to be permanently stable. This preparation appears, likewise, to have all the desirable features of such an iron preparation with but few of the undesirable features. It incorporates a form of iron which, clinically, meets all the requirements necessary in treating the typical iron deficiency anemias but having the undesirable feature of possible gastro intestinal upset—a characteristic of all iron preparations commercially available today. Chemically, it meets all the requirements needed to insure its stability. We have found a minimum amount of ferric ion present after manufacture and the quantity does not increase perceptibly after long periods of storage. It is appealing to the esthetic senses. Thus, pharmaceutically, it is, in our estimation, near perfection.

REFERENCES

(1) Christian, H. A., "A Sketch of the History of the Treatment of Chlorosis With Iron," *Med. Lit. & Hist. J.*, 1 (1903), 176.

(2) Halfer, G., "Le Fer dans le Sang Chez les Enfants," *Arch. de Med. d'Enfants*, 33 (1930), 659.

(3) Heath, C. W., and Patek, A. J., "The Anemia of Iron Deficiency," *Medicine*, 16 (1937), 267.

(4) Reznikoff, Paul, and Goebel, W. F., "The Use of Ferrous Gluconate in the Treatment of Hypochromic Anemia," *J. Clin. Invest.*, 16 (1937), 547.

(5) Mackay, H. M. M., and Jacob, L. E., "Ferrous Sulfate Mixture for the Treatment of Nutritional Anemia in Young Children," *Lancet*, 2 (1937), 570.

Hydrogenated Castor Oil as an Ointment Base

V. Jellified Ointments*

By George W. Fiero†

For certain types of ointments, an occlusive ointment base is desired. The most commonly employed occlusive ointment base is petrolatum. Unfortunately, this base has been used to a large extent without regard to its occlusive properties largely because of the fact that it is stable and has the proper consistency. For certain purposes, a liquefying gelatinized ointment base would be desirable.

In a previous paper (1), the writer discussed the properties of salts of hydroxystearic acid obtained from completely hydrogenated castor oil. This fatty acid has been found to have the peculiar property of producing solid gels when dissolved in oils, either liquid petrolatum or fixed oils, and hydrocarbons such as petroleum distillates, oil of turpentine, etc. By varying the amount of the acid, the consistency of the gel may be governed, and gelatinized ointments of various types may be obtained.

Cosmetic products prepared with liquid petrolatum and hydroxystearic acid possess desirable qualities of softness whether emulsified or non-emulsified, liquid or solid. Thus cold creams containing hydroxystearic acid have a soft jelly-like consistency which is highly desirable.

Liquefying creams can be obtained by

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