In addition to the use of hydrogen peroxide 3 per cent as the oxidizing agent, a solution of 30 per cent strength was also used. This solution of high concentration caused such a violent reaction that it had to be added very carefully and slowly. About 15 ml. of the stronger solution oxidized 100 Gm. of the ferrous chloride solution. This reduced the amount of evaporation necessary to make the finished product weigh 100 Gm. However, we feel that the 3 per cent hydrogen peroxide is the one to be preferred in making this preparation.

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GRAPEFRUIT, CITRUS GRANDUS, C. DECUMANA AND RELATED SPECIES AS A PHARMACEUTICAL FLAVORING AGENT AND VEHICLE.*

BY DAVID J. MASON.[1]

PART I.

The present trend in pharmaceutical vehicles is toward the natural fruit flavors. The recently popularized SYRUP OF CHERRY N. F. VI is an indication of how readily our medical colleagues will seize an opportunity to minimize the patient's resistance to unpleasant tasting medication. While there is no lack of flavoring vehicles to mask harsh-tasting active principles, we must admit that the superiority of one vehicle over another varies with the drug under consideration and the individual's taste. Hence, any increase in the physician's repertoire of pharmaceutical flavoring vehicles should yield a proportionate increase in the number of nasty tasting medications that can be "brought under control." Because of the abundant national supply, its relative lower cost and its pleasant-tasting constituents and aroma, the author sees in the grapefruit, a potentially new pharmaceutical vehicle.

A search of the pharmaceutical literature reveals that no work has been done upon grapefruit as a flavoring vehicle and because of some pleasant experience the author has had with this flavor he thinks it is advisable to further investigate this matter. To present the subject properly the author plans to cover its various aspects in a series of papers. This paper, the first of a series, will concern itself with the bibliography, a description of the chemical and physical properties of the grapefruit constituents, and the botanical classification.

The grapefruit is variously known as the Pomelo or Shaddock, so called from Captain Shaddock who first brought the fruit from the East Indies. The name Shaddock generally applies to the pear-shaped varieties and the Grapefruit or Pomelo to the round ones.

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Grapefruit is grown mainly in Florida and the desert districts of California, Arizona and Texas. The botanical name of the Florida variety is *Citrus Decumana*. The horticultural race is usually divided into the Pomelo and the Shaddock. The horticultural varieties of the former commercially grown in Florida are Silver Cluster, Triumph, Duncan, Marsh Seedless, Hall and several others. The California and nearby production of grapefruit is largely the Marsh Seedless variety, or *Citrus Grandis* (L) Osbeck. There is also the seeded variety known as Clayson Grapefruit and others, the former, however, is the most important commercially.

Since the United States produces (1934) about 90% of the world's supply of grapefruit, it may be considered essentially as an American industry. Approximately 100,000 tons are processed annually by the Florida canners alone.

A cursory description of the gross anatomy of the grapefruit is helpful. The outer yellowish portion of the rind is called the flavedo. It contains the yellow coloring matter and the oil cells containing the volatile oil. Immediately below this is the white portion of the rind and it is known as the albedo. This contains the bitter glucosidic principle naringin, characteristic of the grapefruit. The remaining inner rind and the cellulose-like, nitrogen-containing membranes which are left after the juice is expressed is known as the rag. It is considered a waste product and is generally used as a cattle feed (24). It has potential use as a raw material source for narangin and pectin (1).

The volatile oil may be obtained in three ways. First, by expression from the whole fruit and by subsequent centrifuging from the combined juices (Pipkin process) (2). Second, by the knife process wherein the peel is cut away by sharp knives and then expressed. The third and most commonly used method is known as the hot peel method. Here the fruit is passed through water at 93–100° C., until the skin puffs (3–5 minutes) and is easily removed, thus resulting in a warm peel for the oil expression apparatus.

Grapefruit oil is a pleasant smelling amber-colored liquid resembling somewhat orange and lemon oils. On standing or chilling a yellowish brown, flocculent precipitate forms, which may entirely disappear on warming. Its refractive index is

$$\frac{d20}{20}\ 0.8563,\ [a]\ \frac{20}{D} + 93.28°,\ \frac{n20}{D}\ 1.4758$$

An analysis of the Florida grapefruit oil by Nelson and Mattern (1) reveals the following proximate composition:

Limonene	90.0%
Waxy materials (non-volatile)	7.5%
Oxygenated volatile constituents and sesquiterpenes	2–3%

These consist of octyl and decyl aldehydes; octylic and decylic acids, probably present as esters; geraneol and octyl alcohol (both free and as acetates); cadinene; also probably a very small quantity of *n*-nonyl alcohol; and methyl anthranilate and citral in small quantities. Pinene, terpineol and decyl alcohol were not found. They find no marked difference between oils prepared by the cold or hot peel methods. They also describe a method and suitable apparatus for preparing a terpeneless oil with a yield of 2.7%. The turpentine taste caused by the oxidation of the limonene is eliminated and a concentration ratio of 37 to 1 is obtained.

The relatively high percentage of aldehydes in grapefruit oil indicates the necessity of protecting the oil from oxidation. It is best kept in small amber-glass bottles well filled, and securely stoppered. On the assumption that the hot peel expression method would include a greater percentage of undesirable nonvolatile matter (waxes, etc.), the author recommends for the present only the cold pressed oil for pharmaceutical compounding.

The albedo of the grapefruit contains the glucoside naringen ($C_{27}H_{32}O_{14}.2H_2O$) and was first discovered by De Vry (3). It is a crystalline lemon-yellow substance,

intensely bitter (4), (5) and can be detected in dilutions of 1 in 10–50,000 parts of water. It is soluble in alcohol, acetone and water. When crystallized from these solvents and dried at 110° C. it melts at 171° C. but when crystallized from water it takes on an additional six molecules of water and the melting point is lowered to 83° C. At 45° C. naringin is practically insoluble in water but as the temperature is raised to the melting point (83° C.) its solubility rapidly increases.

Low temperatures will often cause precipitation of the glucoside in canned juices and fruits, especially if prepared from immature or frozen fruit. This precipitate generally settles to the bottom as a yellowish white sludge. Also sections of the fruit may show light yellow spots resembling molds or the juice may have a milky appearance. This is due to the crystallization of the naringin (4). As the fruit matures the naringin content diminishes (11). For this reason well-ripened fruit is most desirable for pharmaceutical compounding.

Upon hydrolysis with dilute acids, the glucoside yields glucose, rhamnose and naringin. The latter, when boiled with KOH, yields phloroglucin and *p*-coumaric acid. This reaction is used advantageously in treating grapefruit sections before canning to remove bitterness and to soften the section membranes (7).

Pectin is also present in grapefruit residue as calcium pectinate (3–4.5%, see Table I) and is a valuable constituent of jellies and marmalades. Medicinally pectin is used as a hemostatic (6), as a detoxicant (25), and in infantile diarrheas (26). Pharmaceutically it has possibilities as a disintegrant in tablet manufacture (27). The grade of pectin is expressed as the number of parts by weight of sugar that can be made into a good jelly with one part by weight of pectin. The 160-grade pectin was considered standard. The 100-grade, however, has become the most popular commercially. Poore describes (5) an effective method for extracting this pectin.

An analysis of California Marsh Seedless grapefruit juice removed by burring contained 12.1% solids, according to the Brix Hydrometer, and 1.87% of acid giving a ratio of solids to acid content of 6.47 to 1. The following organic acids are present in the fruit and juice (22):

Citric	0.6700	to	1.5810%
Tartaric	0.0003	to	0.0007%
Malic	0.0069	to	0.0163%
Oxalic	0.0022	to	0.0053%

An excellent paper describing the constituents of American grapefruit has been written by Zoller (17).

Various methods have been proposed for testing grapefruit maturity (8), (29). It is the practice to express the ratio of the total soluble solids existing naturally in the juice to the per cent of anhydrous citric acid present. The juice is screened (20–40 mesh) and deærated to avoid incorrect readings (Brix Hydrometer). The exterior color (flavedo) may be expressed as a per cent of the ultimate color of the mature fruit characteristic of the horticultural variety. The maturity standards law specifies, however, that this form of testing may be used only at the time of picking,

TABLE I.—PER CENT ANALYSIS OF CALIFORNIA GRAPEFRUIT PEEL AND RAG COMBINED.

Total solids, vacum at 70° C.	22.02	Crude fiber	2.00
Ash	0.70	Protein (N × 6.25)	1.63
Acid as citric	0.43	Total sugars as invert	8.68
Volatile oil (steam dist.)	0.56	Pentosans	1.31
Ether extract	0.23	Calcium pectate	3.93
		Naringin	0.63

before bronzing has set in, either on the tree or in the packing house. This method probably cannot be relied upon when producers or others resort to artificial coloring with C_2H_4 or other means (21).

For preservation and storage, glass has no particular advantage over tin. The cold pack (cans packed as usual and filled with syrup at 180° F. to produce a partial vacuum, sealed and immediately frozen solid) has been found to best maintain the aroma, taste and freshness of the fruit. The difficulty of maintaining this frozen state continuously during distribution and consumer storage, makes this impractical.

The good preservation of the vitamin C content of grapefruit packed in tin cans may be attributed to the disappearance of oxygen from sealed cans after a few days' storage. The slow evolution of hydrogen from the reaction of the acid upon the metal produces a reducing medium for the storage of the fruit (10).

As a rule grapefruit juice is preserved by pasteurization at 185° F. for 6 seconds and then immediately packed (9). There are firms that produce juice concentrates of about 8–1. They use as preservatives $^1/_{10}$ of 1% sodium benzoate domestically and SO_2 for export. If the juice is properly pasteurized and sealed no preservative is necessary until opened. Likewise if sterile juices are sufficiently concentrated they will not ferment until they become subsequently contaminated and, fermentation even then, proceeds very slowly unless diluted.

Cold storage effectively prevents the deterioration of the fruit but eventually results in the breaking down or pitting of the peel. Below 40° F. flavor improves, the fruit becomes sweeter, and the acid content lower. Bitterness decreases on storage, owing apparently to the breakdown of the naringin (11).

The effects of arsenical spraying of grapefruit trees are interesting (23). In all cases where arsenical spraying has been resorted to, arsenic has been found in the rind, rag and juice. There is a slight translocation of arsenic by the vascular system of the tree. Although the amount of arsenic present in the juice is negligible from a health viewpoint, it reduces acidity from 5–20%, decreases the soluble solids and in some cases, greatly hastens maturation. This enables growers to evade the green fruit laws and fulfils maturation standards of acid to sugar ratio. Fruits so matured are of an inferior nature, lack juice and acidity and are insipid. Many states now prohibit the use of arsenical sprays by denying registration of such insecticides.

High temperature treatment of fruit juices yield an objectionable or at best a "cooked" flavor. In extracting the juice, heavy or excessive grinding or screening should be avoided to prevent the incorporation of peel oil or bitter substance from the peel, rag or seeds. A preliminary washing of the chilled fruit in a dilute solution of Ca or Na hypochlorite (50 p. p. m. of Cl) is desirable. A clear product which retains its characteristic flavor for several months may be prepared as follows (12). The grapefruit is washed, expressed and pasteurized at no higher than 85° F. and then stored at 40–50° F. until a sediment is deposited. The clear supernatant liquid is then mixed with kieselguhr and filtered through a pressure filter, sweetened (to contain 17–20% solids—cane or invert sugar) and blended to taste, again pasteurized and run into sterile containers. It is the practice to add dry sucrose or dextrose to increase the Brix acid ratio to 10–13:1. Such addition must be stated upon the label, however, to conform with Federal Law.

Reaming and sweetening incorporate air into the juice. Heating this juice to remove the air lowers the vitamin C content and damages the flavor and keeping quality. The air is best removed by agitation and vacuum deæration at a vacuum of 27 inches or more.

Amber or dark green bottles are used to mask the separation of solids. Stippled bottles are most satisfactory. Grapefruit juice will darken during storage in glass containers. This can be prevented by deæration and storage at low temperatures (60° F. or less). Storage at below 40° F. has delayed darkening for four years. As yet, no process has been developed which will yield juices exactly similar to the fresh fruit in "bouquet" and aroma. The juice for pharmaceutical compounding is best prepared from the fresh mature fruit or a well-processed concentrate purchased in quantities not to exceed a two or three months' supply.

All equipment (9) coming in contact with juice should be of stainless steel or glass. Blocked tin, aluminum and nickel may also be used but are less desirable. The juice should never be permitted to come in contact with iron, zinc, copper or high copper alloys. These metals injure the flavor, food value and keeping qualities. All equipment should be thoroughly washed and steamed immediately after use and twice daily if operations are continuous.

The bibliography of the Genus Citrus is quite large (13). Of late much has been written on its vitamin content. The vitamin C potency has no direct relationship with the soluble solids, acid content or p_H and does not alter after two months' storage under ordinary conditions (14). Preventative experiments show that the antiscorbutic potency is equal to that of the lemon. Curative tests indicate that it is even stronger (15). The frozen juice has the same antiscorbutic potency as the fresh fruit as indicated by tests on guinea pigs (16). A water-soluble vitamin B has been found in quantity equal in potency to an equal volume of cows' milk. Suitable methods of desiccation does not destroy this potency (18). Morgan and Chaney report a slight amount of vitamin A and B. They claim that considerably more of these vitamins are present in home-made jellies and marmalades than in the commercial varieties which suggests a partial vitamin destruction during processing (19). Vitamin G is also present in small amounts (20). A substance exerting a powerful influence on capillary permeability has recently been isolated. Szent-Gyorgyi and his associates have named this factor vitamin P (28).

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WORKING CONDITIONS IN RETAIL PHARMACY.*

BY WORTLEY F. RUDD.

It is common knowledge that by and large they are frequently intolerable. The subject has been talked to death for generations but to date little has been done to correct much of the evil in them.

If you had for a generation or two sat in a pharmacy dean's office and watched enthusiastic, rosy cheek, ambitious fellows as they graduate, pass the board and go into retail pharmacy, and had made yourself sufficiently interested in their affairs so that they come back to visit and talk things over with you from time to time, you would know what is much on my mind in this connection. Even at the end of the first year their step is a bit slower, some of the color has gone and with it some of their enthusiasm. On their second and third and subsequent visits these changes are more pronounced, and we see these men showing signs of settling down in the company of thousands of cadaverous, complaining, non-coöperative and critical men that fret out their very souls as clerks and proprietors in drug stores all over the nation.

I should preface what I am going to say by stating that I do not belong to that group that believes there is anything whatever inherent in the retail drug business, as such, that justifies in any sense many of the working conditions that do exist. But generally speaking, many of them are bad and somebody somewhere, and at sometime, must make a beginning in a study of the causes that have brought about these conditions and offer practical suggestions for changes.

Certainly the writer has no thought that he is a pioneer in this field. You and I have heard long and earnest disquisitions on the subject and have gone home and

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