

Rutin for the Capillaries

by JAMES F. COUCH

THE PRINCIPAL effect of rutin when taken into the body is to restore the strength of the capillary walls when they become weakened. Rutin is a new, cheap, nonpoisonous drug that comes from buckwheat, tobacco, yellow pansies, and at least 35 other plants. Extensive clinical studies of its use in various disease conditions associated with hemorrhage or weak capillaries have demonstrated the value of rutin in medicine.

In 1936 a Hungarian biochemist, A. Szent-Györgyi, announced that he had accidentally discovered a substance that would restore weakened capillaries to normal. The substance, which he called vitamin P, could be obtained from citrus fruits and red peppers. It was distinct from vitamin C, which had previously been thought to have this strengthening action. Szent-Györgyi and his co-workers began a search for the new factor and soon announced that it was a glucoside termed hesperidin, a well-known constituent of citrus fruits that had been discovered more than a century previously. Further research, however, indicated that the vitamin P activity of hesperidin was due to some other substance, present as an impurity in the original crude crystals. Continuing the search, they prepared a concentrate that contained eriodictin (eriodictyol glucoside), a compound closely related to hesperidin but more soluble in water.

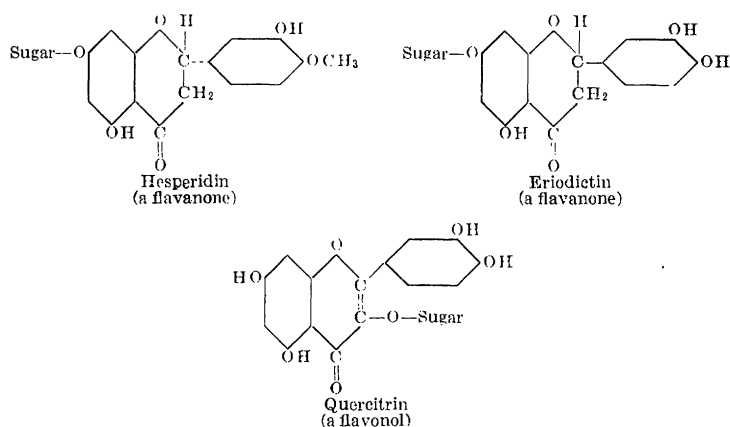
Clinical studies showed this material to be active against increased capillary fragility, but again it was found that the activity was due to some other substance mixed with the crude eriodictin concentrate. Evidence was obtained that a related substance, long known as quercitrin, was present in these extracts. It was subjected to study on guinea pigs and appeared to be inactive. Szent-Györgyi concluded from all his experiments that vitamin C (ascorbic acid) is needed to activate vitamin P

and that when vitamin C is given simultaneously, both hesperidin and eriodictin restore weakened capillaries to normal.

Meanwhile, certain adverse reports were published, but favorable results were reported by scientists in Scotland and England. Many other fruits were studied and several gave evidence that they contained the capillary factor. From the contradictory accounts in the scientific journals, it became clear that the content of active material in the natural products is variable and that some samples may even be devoid of activity. Possibly the active factor is more concentrated at certain stages of growth, or the chemical processes used in concentrating the experimental fruit extracts may damage or destroy it.

The search for the missing factor was continued in various places. A. L. Bachrach and his co-workers in England have contributed extensive chemical studies on citrin and related substances. A. J. Lorenz and L. J. Arnold in California have reported a method of analysis for vitamin P. W. P. Wilson, also of California, has developed a colorimetric method for estimating flavonols. R. H. Higby, in the same laboratory, has studied a soluble form of hesperidin, the chalcone, which he thought might be the active form of the vitamin.

From what was known of the chemistry of the active material, it was evident that this elusive factor was most likely to be of a flavonol structure. The chemical structures of the compounds are similar:



The differences between the flavanone and flavonol structures are slight, but important. The flavonols contain an extra double bond and an hydroxyl (OH) group, which are absent in the flavanones. Because these structures usually confer greater physiological as well as chemical activity on the compounds that contain them, we can expect that the flavonols would be more potent in the body than the flavanones.

The structure of rutin is the same as that of quercitrin, except that the sugar portion of the molecule is composed of glucose and rhamnose,

whereas in quercitrin the glucose is absent and rhamnose alone is present. We reasoned, therefore, that rutin should possess a vitamin P action and might be the long-sought factor. Clinical testing for 4 years has substantiated the conclusion, and rutin is now established as a remedy for weakened capillaries.

Rutin can be prepared in a highly purified condition as a light-yellow, tasteless powder of definite chemical composition. Under the microscope, it appears in characteristic tufts of crystals. It is not toxic. Extensive feedings of large doses to laboratory animals over long periods as well as administration to human patients for many months have shown no deleterious effects.

Thirty-eight species of common plants are known to contain rutin. Among them are buckwheat (*Fagopyrum esculentum*), yellow pansy (*Viola tricolor*), elder (*Sambucus canadensis*), forsythia (*Forsythia splendens* and *fortunei*), hydrangea (*Hydrangea paniculata*), and tobacco (*Nicotiana tabacum*).

At the Eastern Regional Research Laboratory, rutin was first prepared from flue-cured tobacco of high quality. The yield was not large, averaging about 0.4 percent, at a material cost of \$135 to \$150 a pound for the drug. Other types of tobacco, especially the air-cured varieties, were never found to contain more than minute traces. Because of the expense involved in preparing rutin from tobacco, a search was begun to find a cheaper source. Many plants were examined in the laboratory. Several of these, like elder blossoms and leaves, pansy flowers, and white hydrangea flowers, contained enough rutin to be given consideration as possible though somewhat expensive sources.

When buckwheat plants became available, a sample was collected and brought to our laboratory. Analysis showed that it was the most promising plant examined up to then. Further research, including studies of the rutin content of buckwheat at different stages of growth and under varying conditions of handling and storage, disclosed that buckwheat gave a much higher yield (3 to 5 percent) and was so cheap that the material cost of rutin could be reduced to \$1.10 a pound. Ten dollars worth of green buckwheat will furnish as much rutin as \$1,000 worth of tobacco. Besides, buckwheat is a quick crop. In 25 to 30 days after sprouting, the plant contains the highest percentage of rutin, but the greatest yield per acre is obtained 10 to 14 days later, advantage being taken of the extra growth of the plant during that period. This short period of about 40 days from planting to harvest makes it possible to obtain three crops a year from one plot of ground, an economic feature of some importance.

Green buckwheat, however, must be processed within 24 hours after harvesting, because it loses its rutin rapidly when cut. It cannot be dried in the field as hay without nearly complete destruction of the rutin. Even moderately fast drying results in considerable loss of the active constituent.

A process for flash drying has been worked out in which, under certain specified conditions of temperature and air flow, the leaves and blossoms may be desiccated in 45 minutes with a minimum loss of rutin. In this process the stems are not dried but are separated from the leaves and blossoms and discarded.

The dried material may be utilized as a source of rutin. Several solvents will extract the substance. A process has been developed at the Eastern Regional Research Laboratory in which boiling water is used to dissolve out the rutin. Another process, also developed at the laboratory, employs 65 percent alcohol for the purpose. Denatured alcohols or isopropanol can also be used.

When drying is not desirable, the buckwheat can be processed green as soon as it is harvested. The whole plant is submerged in alcohol in a vat and allowed to stand until the next day. The alcoholic solution is drawn off and replaced with fresh alcohol, which is allowed to stand for another day and then drawn off. The alcoholic solutions are distilled to remove the solvent, leaving in the still a mixture of rutin and soluble plant constituents partly dissolved in water derived from the green plant. This is drawn off and cooled. Crude rutin separates out and is collected on a filter. This is now refined by removing the impurities with solvents and recrystallizing until pure rutin remains. The purity of the product is rigorously tested. The over-all yields by this process are somewhat larger than in the procedure that involves drying, because little rutin is lost if the plant is covered with alcohol 3 to 4 hours after harvesting.

Among the other constituents of the plant that are removed from the rutin during refining are some interesting byproducts—sugars, lecithin, sitosterol, and others that may find commercial application.

Rutin was on the market in 1947 in somewhat limited quantities and usually druggists dispensed it only on physicians' prescriptions. Several large manufacturing drug companies entered the field, and plentiful supplies of the substance were expected in a short time.

Clinical investigations of the use of rutin in disease were initiated by Dr. J. Q. Griffith, Jr., of the Robinette Foundation, Medical School, University of Pennsylvania, who has studied its medical applications. Rutin for medical study has been furnished to approximately 400 physicians, hospital clinics, and research workers. A summary of their experience follows.

In patients suffering from high blood pressure there often is rupture of weak capillaries, with production of more or less severe hemorrhage. At times these accidents occur in the retina and cause partial or even complete blindness. Several patients suffering from retinal hemorrhage have been treated with rutin. In 83 percent of the cases, no further rupture of the capillaries occurred. Bursting of blood vessels in the brain leads to apoplexy. Rutin cannot cure the apoplexy once it has occurred,

but it may help to prevent future attacks. In 3 years no patient receiving rutin has had an apoplectic stroke, although all were suffering from hypertension and in more or less danger of such an accident.

An interesting development occurred in the treatment of hypertension. One of the best remedies for high blood pressure has an unfortunate tendency to weaken the capillaries of some patients. This fact forces the physician to use this powerful remedy with great caution in such cases. However, if the patient is given rutin, the tendency to weakening of the capillaries is counteracted, and the physician may proceed with his treatment. Similar effects have been noted in connection with the therapeutic use of salicylates and arsenicals, which also tend to weaken the capillary walls.

Although rutin itself is not advocated as a cure for hypertension, a drop in the blood pressure has been noted in 36 percent of the cases under observation. In 6 percent, the decrease was marked; in the remainder, it was moderate. There is a possibility that rutin may be of value in the treatment of diabetic retinitis, a condition that frequently occurs in diabetes and involves bleeding in the retina. Patients with unexplained bleeding from the lungs, not due to tuberculosis, have been relieved by rutin.

Rutin acts like a vitamin in that it restores these conditions to normal, but the affliction may return if rutin is discontinued. Persons who have a natural tendency to increased capillary fragility often relapse some weeks after discontinuing the remedy.

THE AUTHOR

James F. Couch, a native of Massachusetts and a graduate of Harvard University, received a doctor's degree from American University in 1926. In the Bureau of Animal Industry, 1917-40, he did research on the chemistry of poisonous plants, locoweeds, larkspur, lupines, milksickness, and cyanide poisoning. Since 1940 he has been a chemist in charge of the tobacco section in the Bureau of Agricultural and Industrial Chemistry.

FOR FURTHER READING

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