SCIENCE OBTAINED DRUGS FOR THE VASCULAR SYSTEM FROM THE FLAVONOIDS AND SAPONINS OF PLANTS

Ernesto Riva

In the early 18th century, the Italian chemist Francesco Canzoneri isolated a pink "shapeless mass" with a sweetish taste from the fruit of the horse Chestnut (*Aesculus ippocastanum* L.), which he called esculin: "Not knowing as yet the uses to which esculin or its salts can be destined, we will wait for time and experience to teach us the utility which can be obtained from it", Antonio Cattaneo then wrote in the "Giornale di Framcia e Chimica" in 1825[1].
The discovery however, initially of little pharmaceutical interest, then opened up the way to the chemical and pharmacological study of that numerous and complex group of substances common as pigments in many higher plants: the so-called *flavonoids*.
These are substances the biological meaning of which is not yet completely clear; however, they definitely play a vital role for the life of plants as they take part in the oxido-reductive process of cells, hence the idea to use them in therapy as drugs that can reduce the fragility and permeability of the capillary walls of cells, as well as increase their resistance. *Rutin* (quercetol-3-rhamnoglucoside) is certainly to be considered the ancestor of these drugs: it was obtained in 1842 from the leaves of *Ruta graveolens* L.
The plant was already well known in Antiquity by the name of *pégamon*, given to it by Theophrastus who attributed to it the extraordinary power of inhibiting the germination of seeds and preventing the procreation of other plants, thus giving rise to a whole series of beliefs on the more or less magic powers of the plant, which fuelled popular traditions for many centuries without even sparing classic medicine. Hippocrates, for example, as well as prescribing rue in the treatment of attacks of hysteria, recommended women who wished to become pregnant to introduce rue leaves into their ears and nostrils. The belief that the plant could ward off evil demons was very widespread, especially in the Middle Ages, amongst the populations of Central Europe where they used to prepare wreaths of rue to place on graves and the church altars on Ascension Day and then keep them at home as talismans. All this was done on the basis of the principle that the cross-like shape of the flower of the rue, a manifestation of divinity, had the value of actively exorcising evil spirits. Not even the Salerno school of the 9th-10th centuries was spared from this sphere of witchcraft, considering rue an definite antidote against all poisons: *"… ruta, pyra cum theriaca prestant antidotum contra letale venenum"* and a potent aphrodisiac remedy *"… ruta viris coitum minuit, mulieribus auget…"*. However, the fame of this plant was not only accompanied by magic and miraculous healing which, in parallel with its halo of enchantment, was also officially appreciated and used for its unquestionable therapeutic efficacy.
Hippocrates included rue in his work *Of Illnesses*, amongst the astringent and curative medicaments of troubles of the liver and considered it, above everything else, an irreplaceable remedy to cure menstrual pain and regulate the "lochia" after delivery.
Galen also held the plant in high consideration as a diuretic, bitter, digestive and carminative medicament, whilst Cato the Censor suggested its use, in his *De re rustica*, to heal sores and medicate ulcers.
In the 13th century, the Paduan doctor Pietro d'Abano, referring to the fact that patients before taking medicaments often had a so-called "restorative" bath that was to open the pores to release the humours, recommended taking rue to complete this action. Lastly, in the 19th century, rue officially entered medicine as an emmenagogue, but without overlooking its possible toxicity; it was mentioned in the pharmacopoeias of the time as follows: *"… in medicine its leaves are considered as irritant and stimulant and suitable for encouraging the menstrual flow as they have a peculiar action on the uterus. But rue is a medicament to he used with circumspection, as it may provoke not only menstruation but a dangerous haemorrhage and miscarriage in other cases"*. The most important active ingredient of rue is however the glucoside with a flavonoidic structure called rutin which, thanks to its Vitamin-P-similar activity, can restore capillary resistance to its normal value and is therefore used in the prevention and therapy of hypertensive forms prone to haemorrhaging due to increased capillary fragility.
The leaves of *Ginkgo biloba*, a dioic arboreal plant of large dimensions, originally from the furthermost regions of the East but widely grown in Europe, have also been the object of recent pharmacognostic studies which have highlighted substances of a flavonoidic nature such as ginkgetol and isoginkgetol which are believed to have the characteristic of acting on the peripheral microcirculation, significantly improving it and bringing considerable benefits to peripheral vasculopathies with an ischermic and thrombotic tendency[2].
The only living representative of the order of the Ginkgoales, the Ginkgo biloba is a tree that is still considered today a sort of "living fossil" and in the distant Mesozoic period is believed to have covered vast expanses of the Tyrrhenian islands. It is nevertheless believed that the plant is originally from eastern Asia, where it still grows wild, keeping its ancient typical characteristics unaltered, undergoing a slow evolution in the conformation of its leaves and its sexual apparatus.
This tree is considered sacred both in China and Japan, possibly due to its exceptional longevity and it is usually grown near temples where today specimens of two thousand years old can still be found.
In the early 18th century, the traveller Kaempfer returned to Europe enthusing over the majestic appearance of these sacred trees that he had seen in China and subsequently the plant was also grown in Europe exclusively for ornamental purposes and "officialized" by Linnaeus in 1730 with the name of *Ginkgo*.
However, the plant is highly appreciated in the east as a stimulant for the epidermis and the mucous membrane and the Chinese take the "almond" contained in the sclerotesta of the seed in order to obtain an astringent, sedative and anti-tussive effect in asthma[3]. This aroused the curiosity of modern pharmacology which identified – especially in the leaves – active ingredients with interesting vascular effects.
The ginkgosides act by inhibiting the factor of platelet activation thus reducing the risk of thrombosis and improve the vasomotory regulation associated with the adrenergic functionality, thus beneficial for *memory disorders* and *vertigo* in the elderly.
The bisflavonoids of ginkgo also act on the cellular membranes, stabilizing them and blocking lipidic peroxidation and free radicals and for this reason they are used in cosmetics to *regulate secretions* in the *treatment of devitalized, dry and senescent skins*[4]. The flavonoids of bilberry on the other hand, have been found to be more specifically indicated in the therapy of troubles of the sight, although in the history of medicine there is no application of this type.
It is known for certain that the Nordic peoples used the fruit of the bilberry to obtain colouring matters which they used to dye the clothes of slaves purple and they also fermented and distilled the berries obtaining a very pleasant eau de vie. Otherwise, the plant remained almost unknown in the history of ancient medicine, Even Mattioli in his "speeches" mentioned the bilberry without concealing his ignorance on the therapeutic uses of the plant: *"… in Germany and Bohemia where no species of myrtle grows, the majority of chemists use in their place a plant they call bilberry … this produces berries which, in their colour and appearance, are not unlike those of juniper but are full of a wine-like juice with a sharp taste. In Germany, together with the whole plant, are used instead of myrtle…. some use them to dye yarn and paper light blue. They are also eaten by shepherds and by many others like strawberries as in Bohemia they are sold to the public in the squares because they are not unpleasant to the palate"*.
In actual fact, the interesting properties of the leaves and the fruit of the bilberry were studied from the beginning of the 20th century immediately after the discovery of the active ingredients. An anthocyanic glucoside, chemically identified as the 3-glactoside of delphinine, and defined myrtillin, has been isolated both from the fruit and the bilberry leaves, as well as tannins, sugars and organic acids. Recent studies have shown an outstanding action of the bilberry anthocyanosides on the regeneration of the retinal purple with a marked improvement of the curve of adaptation to darkness and a significant increase in the extension of the field of vision. They are believed to act by accelerating the transformation of the trans-retinene into cis-retinene allowing the regeneration of rhopsodin and thus modifying the structure of the rods that would thus be richer in retinal purple. For this reason, total extracts of bilberry are used in the treatment of severe myopia and reduced crepuscular or night vision.
Another aspect of particular pharmacological interest was triggered off by experiments by various researchers on the vasoprotective activity of bilberry preparations. The anthocyanosides of bilberry, due to their chemical structure – as is known – come under the general category of flavonoids and more specifically the group of Vitamin P factors; this means that they have a marked anti-permeabilizing vassal activity and considerably increase capillary resistance by reinforcing the walls. The use of flavonoids obtained from the leaves of witch hazel (*Hamamelic virginiana* L.) is also very widespread in therapy and, accompanied by an important presence of tannins, succeed in showing a particular tropism on the cellular membranes of the vascular walls and encourage the stabilization of the membranes by exercising a vasoprotective action that is useful in vasculopathies and an astringent and re-epithelizing action useful in dermatitis of an allergic type. The tree called Hamamelis, which grows wild on the eastern coast of North America, vaguely resembles the hazelnut and the native Indians of America knew it very well for the cicatrizing properties of its bark. The Indians also attributed to the plant in the past an extraordinary magic power to the extent of considering it a "tool of work" for the witch doctors during their propitiatory practices.
The discovery of hamamelis by the scientific world, however, is relatively recent and dates back to 1731, when Mark Caterby mentioned it in his *Natural History of Carolina, Florida and the Bahamas Islands* and introduced it to Europe to become mainly an ornamental plant.
On the other hand, with time the *virginiana* variety took on increasing importance from the medical point of view because, as is known, its bark and leaves have considerable astringent and haemostatic properties. This was shown however only at the beginning of the 20th century, when it was possible to identify the particular flavonoidic nature of its active ingredients in the leaves and the bark of witch hazel.
The presence of flavonoids (3-galloil-flavon-4-ol) and triterpenic compounds, as well as of soluble tannins, contributes to the regulation of the muscular tone of the venous walls compromised during inflammation[5].
The heterosides of a flavonoid nature are therefore drugs with interesting biological properties linked to the metabolism of the hyaluronic acid of the precapillary tissues, the factor of permeability of the cellular membranes and the mechanism of saving and boosting ascorbic acid: all these mechanisms lead to the repair of the vascular tissue. All this is thanks to the discovery of that "shapeless mass" obtained by Canzoneri more than a century ago in the fruit of the Horse Chestnut, which had no end of pharmacological surprises in store as it brought to the light another group of substances that proved to be very effective in the treatment of microcirculatory troubles: saponins.
The saponin par excellence was that extracted from *Saponaria officinalis*, a plant that has always been known for its "foaming" properties, however the most widely used and experimented in therapy was certainly escin, obtained from the fruit of the *Aesculus ippocastanum* L.
The history of the horse chestnut begins in the 16th century when the plant – originally from Asia Minor – was imported to Europe to adorn our parks. The etymological meaning of the term ippocastanum is explained by Mattioli saying that *"…they are called horse chestnuts in Constantinople because they are given to horses to eat when they suffer from coughs. The excellent doctor Guglielmo Quac-celbeni Giammengo sent me a branch with shells full…"*.
In the 18th century the plant was appreciated by doctors as an anti-pyretic in place of quinine, but it was above all Giovanni Girolamo Zaniuchelli (1662-1729), a chemist from Venice, who contributed to diffusing its therapeutic use, recommending it for hemicrania and for the treatment of recurring fevers. Afterwards, the use of the horse chestnut was almost completely abandoned, at least until the beginning of the 20th century, when the therapeutic properties of its fruit was valorised following the discovery of its active ingredients with a vasoprotective action. They are saponinic substances or raw saponins, the most important active ingredient separated to date is escin, which by forced hydrolysis can be reduced to the compound escigenin and which can be chemically defined as a pentacyclic triterpene, belonging to the group of bet-amirine-oleanolic acid. Some authors maintain that escin has a good inhibiting activity on experimental oedemas and this is due to the diminished capillary permeability associated with their modest vasoconstriction. The active ingredient is particularly effective against inflammatory reactions, especially if of the allergic type, with a mechanism that appears to be mediated by the adrenal glands. On the basis of these observations, escins would be indicated in the therapy of post-traumatic oedemas, thrombolytic oedemas, varicose syndromes and rheumatic disorders characterized by inflammation and oedema. On the other hand, experiments on the saponins contained in Centella asiatica (*Hydrocotile asiatica* L.), better identified as asiaticosides, are only recent.
The people of Malaysia have always known a medicinal plant called "tiger grass" with which, according to local legend, tigers "medicate" the wounds inflicted on them during fights with other animals by rubbing themselves on grassy expanses covered with this plant, which is, in fact, widely used in popular Indian medicine as a cicatrizant and under the Sanskrit name of Mandukaparni is indicated as a specific remedy against leprosy. In the 17th century this medicament with a lasting fame as a cicatrizant also aroused the curiosity of the colonial world and the Dutchmen Rhumphius and Rheede, botanists in the colonial services, were the first to introduce the plant to the Western world[6]. It is the now famous Centella asiatica, thus called perhaps from the Italian verb "centellinare" (to sip) which refers figuratively to the continual "sipping" of the plant in the marshes where it lives. The most widely adopted scientific name, especially in the 17th century, was that of Hydrocotyle (idro = water, kotyle = bowl), with a reference to the peltate form of its leaves which are easily filled with water like a bowl.
Centella then gained the fame of a universally recognised official medicament when, in the 19th century, a doctor from the island of La Réunion in the Indian Ocean, followed the example of local empirical medicine and successfully cured the leprosy that he had contracted during his frequent contacts with the patients he himself was trying to cure. Since then, and the merit goes especially to colonial doctors, Centella continues to be successfully experimented against the most frequent diseases of the skin, including leprosy, lupus and scrofula.
At the same time, the first attempts to isolate the active ingredients responsible for the therapeutic action were made, but it was not until the mid twentieth century that the final chemical configuration of the asiaticosides contained in Centella were known. This discovery gave rise to a long series of research and experimentation which did no other than confirm the important role of Centella in empirical Indian medicine.
The leaves of Centella have a high content of triterpenic saponins, better identified as asiaticosides, asiatic acid and madecassic acid, They also contain flavonoids in a free and glucosidic form, phytosterols and tannins. Without doubt, the most interesting active ingredients are in the triterpenic fraction, namely the asiaticosides and their isomers and these have been the object of countless pharmacological studies.
Their remarkable tropism on the connective tissue leads to a stimulation of the endothelial reticulum with a significant growth of the fibroblasts and the fundamental amorphous substance represented by the glucosaminglycans. The result is that the cicatrisation processes of the wounds are encouraged and more in general all those phenomena that are consequent to a breakage of the homeostasis of the connective tissue are normalised.
The place of action of the asiaticosides is therefore on the connective tissue, where the production of collagen is regulated, when this is altered, by mean of the formation of two fundamental amino acids that are alanine and proline.
After thus normalizing the physical-chemical state of the fundamental substance, Centella finds a specific indication in venous insufficiency, of which it slows down the evolution and prevents the dystrophic complications attributable to an altered venous circulation. A considerable amount of clinical work has shown the value of these active ingredients in the field of phlebology; Centella can therefore slow down the evolution of the venous disease, significantly improve its symptomatology, prevent dystrophic complications and suppress functional disorders.
All this takes place with a significant increase in the elastic contention of the venous connective sheaths and an increase in the return venous circulation also due to an induced reduction of platelet activity. It can therefore be understood how therapeutic treatment with preparations of Centella asiatica makes a considerable contribution to reducing venous stasis and preventing deep venous thromboses[7].