Chemické Listy

Review

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STRONG WILLOW BARK BREW

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The story of aspirin is exciting and complicated. We tried to decipher the role of the main characters, as well as a wide field of pharmacological roles of acetylsalicylic acid, a super-drug, which would not be approved by responsible institutions today but which is still one of the most used medicines on the Earth, as well as in the space (it was used by the astronauts in the Apollo project). Original literature sources were used as much as possible to clean up some misinformation around the topic. The authors are aware that Aspirin is a trademarked name but it has become "popular" in common human speech.

Keywords: history, aspirin, acylpyrin, acetylsalicylic acid, salicin, E. Stone, P.-J. Leroux, J. A. Buchner, R. Piria, C. F. Gerhardt, A. E. Eichengrün, F. Hoffman, H. Dresher, J. R. Vane

Fig. 1. ***Salix alba***

Remarkably, the history of aspirin goes back as far as 3500 years. The substance belongs to a group of compounds called "salicylates", the simplest of which is salicylic acid. Plants containing these compounds (including conjugates such as glycosides and esters) are found all over the world, for example, white willow (*Salix alba*, Fig. 1, ref.[1]), common myrtle (*Myrtus communis*), meadowsweet or mead wort (*Filipendula ulmaria*) and many others. Many of the world's oldest civilizations recognized the medicinal value these plant drugs have and used them to treat various ailments. For example, the Ebers Papyrus, an ancient Egyptian medical text from around 1550 BC, describes the use of willow and myrtle to treat fever and pain[2]. The ancient Sumerians used willow bark as a medicine, e.g. against pain[3].

Hippocrates himself advocated the use of willow bark tea with an astringent taste[4] (however, the astringent taste is not due to salicylates or salicin, although this is also bitter, but primarily to the content of tannins, which can be up to 10 %) to reduce fever and relieve pain, thus at birth. Dioscorides recommended an infusion of willow (*Itea*, the name in the cited edition[5], transcribed into Latin is

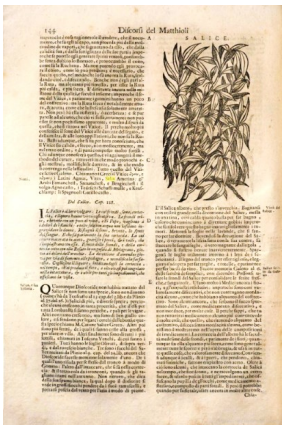

Fig. 2. **Matthioli willow decription**

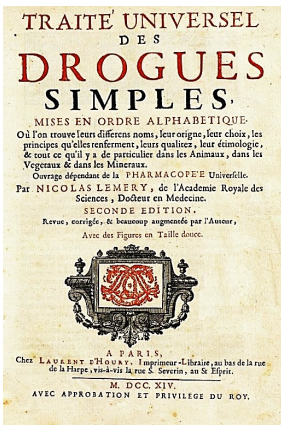

Fig. 3. **Lemer book frontispiece**

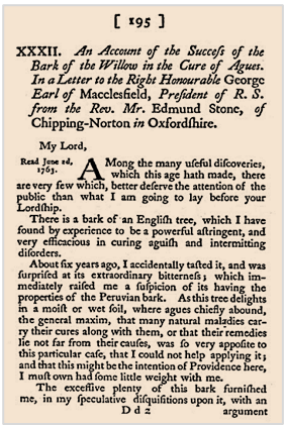

Fig. 4. **Stone willow decription**

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confusing, the correct name should be the Greek name *ιτιά* transliterated into Latin *itiá*) as an analgesic, which Matthioli also did[6]. Saint Kevin of Glendalough (Cóemgen), an Irishman living in the sixth century AD, became famous within the of old non-antique Europe for the use of willow decoction[3].

In the 17th century, Nicolas Lémery (1645–1715) in his book[7] on simple drugs, first published in 1698, describes in particular the "febrifuge" (i.e. fever-repelling, antipyretic) character of willow. An old Czech folk guide used a decoction of willow bark[8] for gynecological problems, scabies, ulcers, etc., as well as the above-mentioned Matthioli (salice)[9]. At other times, it is recommended against nosebleeds[10], colds[11], diarrhea in domestic animals[12], to treat hemorrhoids[13] and jaundice[14], and sometimes bitter willow bark was added to beer[15].

The leap forward to modern times was the first ever recorded clinical study of willow bark, when in 1763 the Reverend Edward Stone of Chipping Norton (1702–1768; sometimes mistaken for the mathematician Edmund Stone[16]), an Oxford naturalist, clergyman and fellow of Wadham College, University of Oxford, was looking for a remedy for the symptoms of malaria[17]. He found a promising remedy in ground willow bark, which he studied for its bitter taste (it reminded him of cinchona bark). Later, the physician Samuel James (ca. 1763–1831) wrote a book[18] *Observations on the Bark of a Prarticular Species of Willow* ... where he recommends a decoction for various types of fevers, vaginal discharge, abscesses and bleeding. A similar book[19] was published in 1798 by William White, a doctor from the city of Bath. As their follower, we have a documented case where the doctor George Wilkinson (1752–1831) also treated typhus[21] with a decoction of willow bark[20]. He tried to popularize this remedy and even sent out a sample of the bark[22] with an explanatory "circular" to British doctors. But it took almost 100 years for science to reveal its secret.

In 1825, Francesco Fontana (1794–1867), a pharmacist from Lariza near Verona, isolated an impure active substance from white willow and called it salicin[25]. Shortly thereafter, supposedly inspired by Wilkinson's work, a pharmacist from Vitry-le-François, Pierre-Joseph Leroux[26,27] (1795–1870; in the literature sometimes Le Roux, Roux L. G., sometimes Roux L. E.) isolated pure salicin from willow bark, which he published[28] in 1830. The isolation is also attributed to Johann Andreas Buchner (1783–1852; sometimes just A. Buchner, J. Büchner), who allegedly isolated a year earlier (also published in 1830, but later than Leroux) "a bitter substance from willow", salicin[29], as his son[30] L. A. Buchner writes in the paper[31] "*Zum 104. Geburtstag von Johann Andreas Buchner*". However, Leroux managed to obtain the bitter substance of willow bark in a crystalline state[32], and since he presented it in greater quantities and in a pure form, and described its properties in more detail in a paper sent to the Académie royale des sciences[33], Fontana not even Buchner are not mentioned as the discoverers of salicin in most chemical works, but Leroux. Interestingly, the Chemisches Zentralblatt reminds in the editorial note[29] that Buchner did not know about Leroux's discovery, one may fear that this is a small support to a colleague.

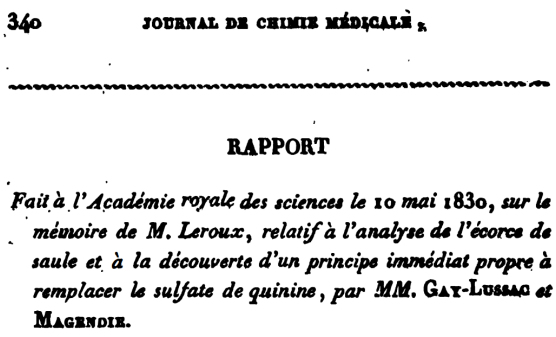
Charles Leroux[36], who was an American inventor, balloonist, and parachutist, or Charles Henri Leroux, Parisian physician[37], chemist Henri Leroux[38], and many others are often mistakenly cited as the discoverer of salicin in the literature. Citation "Leroux H.: J. Chem. Copper. 6, 341 (1830)", which numerous authors copy from each other, cites the work of "Mr." Leroux (M. Leroux) is most likely a misquotation of the article by Gay-Lussac and Magendie[33].

Fig. 7. **J. A. Buchner**[34]

Fig. 8. **P. J. Leroux**[35]

Fig. 5. **G. Wilkinson**[23]

Fig. 6. **F. Fontana**[24]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RAPPORT

Fait à l'Académie royale des sciences le 10 *mai* 1830, *sur le mémoire de M. Leroux, relatif à l'analyse de l'écorce de saule et à la découverte d'un principe immédiat propre à remplacer le sulfate de quinine, par MM.* GAY-LUSSAC *et* MAGENDIE.

Fig. 9. **Abstract of the Gay-Lussac and Magendie paper**[33]

Obr. 10. **R. Piria** (Wikipedia)

Obr. 11. **A. Cahours** (Wikipedia)

Raffaele Piria (1814–1865), an Italian chemist working in Paris, 1838 hydrolyzed salicin from extracts obtained from willow bark into a sugar and an aromatic component ("saligenin"), which he oxidized into an acid he named "Salicylwasserstoff", salicylic acid[39,40]. However, it turned out to be toxic and caused stomach problems.

Outside the competition, another French pharmacologist, Auguste André Thomas Cahours (1813–1891), proved in 1844 that the oil of eastern teaberry, checkerberry, boxberry, or American wintergreen (*Gaultheria procumbens*), a traditional remedy for diseases such as colds, contained salicylic acid methyl ester[41].

When applying decoctions from, for example, willow bark, it was believed that salicylaldehyde was released by hydrolysis of the glycoside under the action of hydrochloric acid in the human stomach and was gradually partially converted to salicylic acid by oxidation. It's a bit complicated, L. A. Buchner also in the mentioned article[31] relates salicin (2-(hydroxymethyl)-phenyl-β-D-glucopyranoside) and helicin (2-formylphenyl--β-D-glucopyranoside), but what exactly was the matter at the time, it's hard to find out.

In the nineteenth century, pharmacists began experimenting with various compounds related to salicylic acid. In 1853, a Frenchman from Alsace, Charles Frédéric Gerhardt (1816–1856), prepared and a year later published

Pharmaceutisches

Central Blatt.

15. Juni 1839. №. 24.

Redaction: Dr. A. Weinlig und Dr. E. Winkler.

INHALT. Salicin und seine Produkte von Piria und Dumas und über salicylige Säure von Ettling. — Künstliche Bildung des Chlors auf galvanischem Wege von Reinsch.

Kl. Mitth. Darstellung von kryst. Schwefelnatrium. — Kiesteine. — Meconsaures Morphium. — Veilchenzucker und Veilchensyrup. — Kohlens. Cinchonin und Chinin. — Zersetzungsprodukte des xanthogens. Bleioxyds und Kali's. — Blut bei Amenorrhöe. — Corrigans Apparate zu Inhalationen aller Art. — Jod im Leberthran. — Trennung von Kobalt und Mangan.

Ueber Salicin und seine Produkte von Piria und Dumas und über salicylige Säure von Ettling.

Fig. 12. **Title of the original Piria paper**[40]

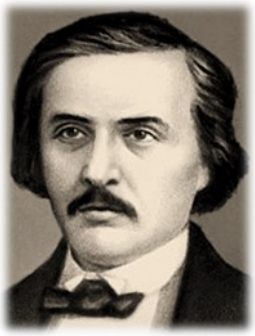


Fig. 13. **C. F. Gerhardt** (Wikipedia)

Fig. 14. **A. E. Eichengrün** (Wikimedia)

the preparation "wasserfreie Salicylsäure-Essigsäure", or acetylsalicylic acid[42]; an alternative procedure was published by the Austrian Hugo von Glim[43]. In 1892, Paul Freer published a paper where he mentions the reaction of *i.a.* acetyl chloride and salicylic acid[44]. Chemical Abstracts cite G. C. Foster's 1860-1861 publication as the earliest work mentioning acetylsalicylic acid; however, we were unable to identify the mentioned substance in the original work[45], however, in the mid-nineteenth century it was hardly possible to talk about nomenclature.

But it took almost half a century again before the chemist Arthur Ernst Eichengrün (1867–1949) and his colleagues, in 1897, convinced several pharmacologists to test the preparation and finally the German company Friedrich Bayer & Co. in Elberfeld (where they were employed in the pharmaceutical laboratory of this company specializing originally in the production of paints) to bring this drug to market. Acetylation seems to had been popular with Bayer, they developed cellulose acetate here, but they also worked with heroin (diamorphine = diacetylmorphine) and not surprisingly they also acetylated salicylic acid. The Jew Arthur Eichengrün later left Bayer to make a career "for himself" as an entrepreneur producing the aforementioned acetylated cellulose (until 1938, when he was aryanized). He was later imprisoned and "forgotten" under Reich law. Eichengrün's collaborator and (according to some authors) "technician or laboratory worker" Felix Hoffman (1868–1946) allegedly appropriated[46,47] the "invention", saying that he developed the substance because his father was said not to like the bitter taste of sodium salicylic acid, which he used for rheumatism. The position of a laboratory technician working under Eichengrün is at least questionable with Hoffmann because Hoffmann had a doctorate from the University of Munich, even "*magna cum laude*" and was practically the same age[48,49].

Fig. 15. **F. Hoffmann**[49]

Databáze terezínských vězňů a osob deportovaných do ghett Łódź, Minsk a do pracovního tábora Ujazdów	
Jméno	Arthur Ernst
Příjmení	Eichengrün
Datum narození	13. 8. 1867
Titul	Dr. phil. Ing.
Označení transportu do Ujazdówa (1942) a ghett Łódź (1941), Minsk (1941), Terezín (1941-1945)	I/112, 26. 5. 1944, Berlín → Terezín, 32?
Transportní číslo do Ujazdówa (1942) a ghett Łódź (1941), Minsk (1941), Terezín (1941-1945)	14780
Místo osvobození	Terezín
Osud	Přežil/a

Fig. 16. **Excerpt from the database of Terezin prisoners**[52]

Eichengrün, who returned home from the Terezin concentration camp, claimed the discovery in 1949, saying that Hoffmann, who had died shortly before, was working according to his instructions and did not even understand what he was doing and why, but he also died shortly after that on 23. 12. 1949 at the age of 82, in Bad Wiessee in Bavaria[50]. Before his death, Eichengrün wrote that his goal was to obtain a derivative that would not cause side effects (stomach irritation, nausea, or tinnitus) that were often associated with sodium salicylate[51].

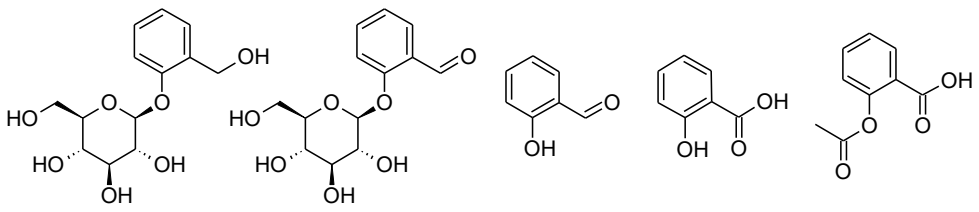
On a side note, it can be mentioned that Heinrich Dreser (1860–1924), head of the experimental pharmacological laboratory in Elberfeld, allegedly experimented with acetylsalicylic acid as early as 1897,

Fig. 17. **H. Dreser in his laboratory** (second from right; Wikimedia)

Fig. 18. **Bayer's Aspirin** (Bayer Co. USA)

but he was not satisfied with the results and abandoned further research into this substance. He only published the story about aspirin later[53], where he supported its alkaline hydrolysis, but also described the positive inotropic activity of aspirin. A wide discussion on the complicated historical topic of the discovery of aspirin itself was summarized and published by Walter Sneader with a conclusion leaning in favor of Eichengrün[54] in the matter of invention rights.

For the substance, the Bayers introduced the name "aspirin" by combining the "a" from acetyl chloride with the "spir" from *Spirea ulmaria*, which is the former name of the plant, now correctly *Filipendula ulmaria* with the English name meadowsweet which in some sources is also referred to as mead wort, from which the Swiss chemist Johann Pagenstecher isolated[55] "spirsäure", which Karl Jacob Löwig identified[56] as salicylic acid, "Salicylwasserstoff". Owing to its very pleasant scent, the wort has long been used as a scented plant for the premises of homes, and it was also added to fruit juices and mead[57]. The Bayers originally obtained salicylic acid from this plant, but it was later (due to unproductive isolation) produced, for example, by the Kolbe-Schmitt reaction from phenol[58]. The suffix "-in" was just a fashionable ending for medicines at the time. In 1898, Hoffmann filed a patent application for aspirin, and in 1900 he finally received a US patent[59], when in the patent application he relied on the fact that Kraut's previous publication on acetylsalicylic acid did not provide a high-quality physicochemical description of it. The matter is interesting because the cited author Kraut did not publish about salicylic acid in the application cited in the journal Annalen der Chemie und Pharmacie, according to Chemical Abstracts, and the paper cited in the patent was not found. Any Kraut didn't even publish any work on



salicin helicin salicylaldehyde salicylic acid acetylsalicylic acid

salicylic acid that could be found in CA. The thought suggests that Hoffmann was a pretty wag. The story is somewhat reminiscent of the story of the awarding of the Nobel Prize for Chemistry in 2022 (ref.[60]).

Our pharmacy workers were well informed and as early as 1899 the journal Časopis českého lékárnictva[61] published the following report (translation):

Newer drugs: Aspirin $C_6H_4\langle^{COOH}_{OCOCH_3}$, acetylsalicylic acid form white needle-like crystals, which dissolve in 100 pt. of water at 37°, more easily in organic solvents. It is used in doses of 4–5 gr, *pro die* (in a daily dose, editor's note) for "hostec" (rheumatism, editor's note) of joints and muscles, as well as *pleuritis sicca* (so-called dry pleurisy, editor's note) and *exsudativa* (inflammation of pleurisy, when a pleural effusion is formed, editor's note). It has the advantage over other salicylic preparations in that it is broken down only in the alkaline intestinal juice, as a result of which it does not irritate the stomach lining. The taste is pleasant and there are no unpleasant side effects. (This is a good observation for its time since deacetylation proceeds well with a catalytic amount of alkali.)

So not to be in conflict here, such as Emil Šedivý, a Prague pharmacist who sold acetylsalicylic acid, and got into a dispute with Farbenfabriken vorm. Friedr. Bayer & Co., which then, after an agreement, withdrew from this name[62], since the time of the first republic, e.g., the joint-stock factory Kolín produced acylpyrin[63], in the name of which we see acyl and antipyretic activity.

Acetylsalicylic acid crystallizes in two crystal forms (dimorphism); form I[64] and form II[65], which are morphologically quite close and which do not necessarily have all the same physicochemical properties equal, and moreover, they can change into each other[66], e.g. during processes such as Viedma ripening[67]. In 2010, a patent application claiming the new[68] polymorph was filed, but apparently the patent was not granted. Bayer AG reportedly markets aspirin in Form I, claiming that it has better bioavailability. Another method of increasing bioavailability is to prepare tablets by co-grinding aspirin and a solubilizing agent such as sodium or calcium carbonate or bicarbonate that coats the crystals. The mixture is then compressed to form tablets that have an improved dissolution profile for the therapeutically active ingredient[69]. The so-called New Aspirin™ contains acetylsalicylic acid in the form of microparticles that have an average of 10 percent of the particle size found in previous Aspirin™ tablets. The microparticles are combined with sodium carbonate, which acts as a disintegrating agent and local buffer, helping New Aspirin™ dissolve faster, enter the bloodstream faster, and relieve pain twice as fast as other tablets with the same active substance[70,71].

According to package leaflets published by SÚKL[72], acetylsalicylic acid is used for the symptomatic treatment of fever and/or mild to moderate pain such as headache, flu syndrome, toothache, menstrual pain, or muscle pain, it also suppresses the inflammatory response; in these cases, a single dose is 400–500 mg. In the case of tablets containing 100 mg of the drug, i.e. in lower doses, it prevents the formation of blood clots. The Czech SÚKL registers this medicine either as a monocomponent or with other medicines of a similar nature (in total, approximately 50 preparations in various strengths and versions are registered). The best-known preparations in the Czech Republic containing acetylsalicylic acid are Acifein, Acygal, Acylcoffin, Acylpyrin, Acylpyrin with vitamin C, Algirin, Anopyrin and Aspirin[72].

In addition to analgesic, antipyretic, and antiphlogistic properties, acetylsalicylic acid also has inhibitory effects on platelet aggregation in low doses. The antithrombotic effect is based on the irreversible acetylation of cyclooxygenase in platelets; the formation of thromboxane A2 is inhibited. In the form of buffered tablets, the drug shows a lower incidence of adverse effects on the digestive system (mainly the stomach).

It is used in unstable *angina pectoris* (supplement to standard therapy), acute myocardial infarction, in the prevention of reinfarction, after arterial vascular surgery or interventional procedures (e.g. after aortocoronary bypass, during percutaneous transluminal coronary angioplasty). It has also found relatively wide application in the secondary prevention of transient ischemic attack and cerebral infarction.

Despite the widespread use of salicylate-containing substances for many centuries, the exact mechanism by which aspirin exerts its anti-inflammatory and analgesic effects (although it is not an analgesic-anodyne) was unknown until 1971. Research by the British pharmacologist Sir John Robert Vane[73] (1927–2004) led to the discovery mechanism of its action and was awarded the Nobel Prize in 1982 for this work.

Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the activity of an enzyme called cyclooxygenase (COX)[74]. COX exists in two isoforms: COX-1 and COX-2, which are responsible for the production of prostaglandins (mainly PGH_2) and thromboxanes (mainly TXA_2), two types of lipids found in almost every tissue in the human body. Prostaglandins are responsible for the transmission of pain messages to the brain and inflammation, while thromboxanes, when released, cause vasoconstriction (narrowing of blood vessels) and clumping of blood platelets, thereby contributing to blood clotting, which causes heart attacks, reducing the production of these intermediates further contributes to the reduction of blood clotting. The acetyl group of acetylsalicylic acid binds irreversibly to the serine in COX-1, thereby inhibiting the production of these lipids. This

Fig. 19. **J. R. Vane** (Wikipedie)

irreversible binding is a factor that distinguishes acetylsalicylic acid from other NSAIDs, as many of them, such as ibuprofen and diclofenac, bind reversibly[75]. Thus, as might be expected, there is substantial evidence that low doses (75–325 mg) of acetylsalicylic acid can be highly effective in preventing cardiovascular events through its antithrombotic effect, as previously reported. Administering acetylsalicylic acid prophylactically before and during a heart attack or stroke (in patients predisposed to the conditions) can save lives, but there are risks associated with bleeding in the brain or stomach, leading many doctors to be cautious about recommending this drug as prevention. To reduce the burden on the stomach, there is also a variant of application through the skin[76] or *per rectum*[77]. For example, the gastroprotective effect of capsaicin from chili peppers (*Capsicum annuum*)[78], alcoholic extract from citron melon (*Citrullus melo*)[79], or the Indian tree *Utleria salicifolia* can be used against the negative effects of acetylsalicylic acid, however curious this literary information is. However, the addition of Ca^{2+} ions, or the formation of a calcium salt, which is the least irritating, or a conjugate with glycine (100 mg acetylsalicylic acid/50 mg Gly) in the form of Godasal, when there is an increase in the solubility and thus the bioavailability of acetylsalicylic acid, i.e. at the same time a possible reduction in irritation[80].

Although there is no conclusive evidence that acetylsalicylic acid prevents the formation of neoplasms, there are many studies that show that acetylsalicylic acid can reduce the risk of their formation[81]. In particular, it is believed that it can work as an adjunctive treatment for breast, prostate, and colon tumors and that the anti-inflammatory properties of this drug can help prevent the spread of neoplastic processes to other parts of the body[82].

Numerous studies show that acetylsalicylic acid can also help in the treatment of COVID-19, possibly due to platelet aggregation. A retrospective study found that those patients already taking acetylsalicylic acid for cardiovascular disease had a 47% reduced risk of mortality and risk of being placed on a ventilator. Even hospital admissions in the first instance were 40% lower. Another study conducted by the University of Oxford found that the blood-thinning properties of acetylsalicylic acid prevented complications from blood clots that commonly occur as a result of COVID-19 (ref.[83]).

Acetylsalicylic acid also reduces vegetative bacterial density, hematogenous spread of bacteria, and the frequency of embolic events in experimental endocarditis caused by *Staphylococcus aureus*, *i.a.* through antibacterial effects[84].

Acetylsalicylic acid is also used against migraine[85], it is reported that it also acts as a means whose aim is to influence the underlying cause of aging and age-related diseases, thereby extending life expectancy[86], but it is reported that it also has teratogenic effects[87] and can be an allergen[88].

In many places, we see warnings against the combination of acetylsalicylic acid and alcohol[89]. Acetylsalicylic acid can alter the absorption of ethanol and the rate of its metabolism. The cause of this phenomenon may be delayed gastric emptying[90] or a decrease in the activity of gastric alcohol dehydrogenase[91,92]. The result is then a faster initial rise in blood alcohol concentration. On the other hand, the preparation Alka-Seltzer, a combined (effervescent) preparation containing acetylsalicylic acid, citric acid, and sodium bicarbonate, which is used as an analgesic-antipyretic intended especially for febrile states in viral respiratory diseases, has gained a reputation as a popular remedy for alleviating hangovers[93]. Acylcoffin, a combined analgesic containing acetylsalicylic acid and caffeine, is also used for hangovers, according to folk healing tradition. On the other hand, in one old study, it was found that a small shot of vodka taken before the administration of acetylsalicylic acid reduced the risk of stomach damage[94].

Ingestion of acetylsalicylic acid, especially swallowing a whole, unbroken, or unquartered tablet without proper drinking, can cause bleeding in the stomach. Acetylsalicylic acid can cause stomach pain, heartburn, nausea, vomiting and ulceration, perforation, and significant bleeding in the digestive tract. Dyspepsia (a general term for various digestive problems; editor's note) is common, but fortunately, pharmacists teach patients what to do in such a case. Patients with a history of active peptic ulcer should avoid acetylsalicylic acid. This substance can also cause hypoglycemia (or hyperglycemia) in children. Epidemiological control studies have repeatedly shown that patients admitted to hospital with acute upper gastrointestinal bleeding, especially patients without radiologically detected abnormality, contain a disproportionately high proportion of individuals who used analgesics containing acetylsalicylic acid[95]. Intolerance of acetylsalicylic acid causes skin and/or respiratory reactions[96]. In general, people over the age of 60 and patients with digestive problems should be on the lookout for stomach bleeding and stomach ulcers, especially in conjunction with a higher dose of alcohol. Acetylsalicylic acid is said to increase blood pressure and may also increase the risk for patients with liver and kidney problems. It can also cause problems for asthmatics. It is contraindicated in patients sensitive to salicylates and NSAIDs. It is also contraindicated in patients with asthma, rhinitis, and nasal polyps. It can cause anaphylaxis, laryngeal (larynx; editor's note) edema, severe urticaria, angioedema (a skin condition with swelling in the subcutaneous tissue in various parts of the body, causing problems), or bronchospasm (asthma). All salicylate products also carry the traditional Reye's syndrome warning to avoid use in children or adolescents who have any viral infection, with or without fever. It is not good, without consulting a doctor, to combine acetylsalicylic acid with blood clotting drugs, antihypertensives, other NSAIDs, or corticosteroids[97]. Acetylsalicylic acid can reduce the effect of angiotensin-converting enzyme (ACE) inhibitors, diuretics, beta-blockers, and uricosurics (drugs that

increase the excretion of uric acid in the urine, such as probenecid and sulfinpyrazone), increase the toxicity of acetazolamide and methotrexate, prolong prothrombin time and bleeding time in patients taking warfarin, increase the anticoagulant activity of heparin, decrease blood levels of phenytoin, increase serum levels of valproic acid, and increase the effectiveness of oral antidiabetic agents to the extent that the patient may suffer from hypoglycemia. Acetylsalicylic acid may increase bleeding or decrease kidney function when given at the same time as other NSAIDs. Already in 1909, however, even Czech pharmacists warned[98] that: "Aspirin, which until now was considered a completely harmless drug, will cause ringing in the ears, headaches, stomach upset and irritation to throw up in many individuals. The formation of various exanthems and enanthems on the skin and mucous membranes can also have an external effect. Sometimes it causes dizziness, and lightheadedness and disrupts the regular heartbeat. Milk and alkaline waters should never be drunk immediately after taking aspirin so that their decomposition does not take place so quickly and violently".

It is known that the combination of aspirin with some other drugs can lead to health problems and even death[99]. Aspirin overdose is very rare, although not impossible; symptoms may include tinnitus (buzzing and whistling in the ears), hyperventilation, vomiting, dehydration, fever, double vision, and feeling faint. The first choice for poisoning is the administration of activated charcoal. Oral toxicity LD_{50} in rats is 1400 mg kg^{-1}. In humans, a toxic dose[100] greater than 500 mg kg^{-1} is assumed. The highest recommended doses reach the value of 77–100 mg kg^{-1} day^{-1}. Older packages of acetylsalicylic acid, especially if they are not kept completely dry, may contain salicylic acid produced by hydrolysis, which is 2–3 times more toxic[101].

In addition to human use, it is known that acetylsalicylic acid can significantly increase stress tolerance in plants such as beans[102], tomatoes[103], peppers[104], sugar melon[105], or tuber growth in potatoes[106] and others in the garden. It also mitigates cold damage and maintains bioactive compounds during pomegranate storage[107]. Folk tradition teaches that if we add an aspirin tablet to the water in a vase, cut flowers will last longer, but the experiment showed that this is probably not the case[108].

It is obvious to be true the bon mot stating that if someone invented aspirin today, no institution would allow its use. It is also worth remembering that it was "promoted" as a female contraceptive under the slogan: "tablet between the knees and hold"; however, the protection was undoubtedly not, as we can imagine, one hundred percent.

In summary, acetylsalicylic acid is an old drug with established use in the treatment of pain, inflammation, and fever, and is increasingly used for the prevention of cardiovascular disease. This drug and other NSAIDs may now face new therapeutic uses, such as the chemoprevention of colorectal cancer, the prevention and treatment of Alzheimer's disease, and the treatment of reflux esophagitis[109].

We present this article as another contribution to a series of teaching texts describing various interesting aspects of the chemistry of natural substances[110–112] also because we want to respond in this way to the amount of fiction, half-truths, and nonsense that are spread today around natural compounds, and especially aspirin.

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