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ORIGINAL ARTICLE

Medicinal potential of willow: A chemical perspective of aspirin discovery

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Abstract The willow tree is a symbolic medicinal plant that has been associated with the discovery of aspirin, chemically known as acetylsalicylic acid, or salicylate, which still offers surprises as a revival drug. The philosophical perspective of the significance of the willow tree has been elaborated since the Assyrians (4000 BC) and Sumerians (3500 BC), who were aware of its medicinal merits. In 1838, the main pharmacologically active ingredient of willow, the salicin structure was elucidated by hydrolysis to comprise *D*-glucose and salicyl alcohol. These uncovered new perspectives, which eventually lead to the discovery of aspirin.

1. Introduction

Over a century, numerous articles have been published on the discovery of aspirin, its profound association to willow tree as well as on its pharmacological significance (Mayer et al., 1949; Lévesque and Lafont, 2000; Jones, 2001; Mahdi et al., 2006). Generally, medicinal plants have contributed profoundly to the development of drugs known of today as to the concept of complementary medicines, the most widely used form of therapeutic intervention in the past to present. Indeed, many well-defined 20th century drugs were derived from herbal plants. Drugs including salicylic acid (*Salix* sp.), curare (*Chondrodendron tomentosum*), digitoxin (*Digitalis purpurea*), taxol (*Taxus brevifolia*), and many others, are well-recognised drugs derived from plants with pharmaceutical and clinical potentials (Ackerknecht, 1973; Sumner, 2000; Dewick, 2002). Some of the mentioned drugs were known even to many early civilisations such as Assyrians and Sumerians (Anderson, 1977; Saggs, 1989; Mindell, 1992; Cunningham, 1996; Riddle, 1999). It is generally accepted that the pharmacological properties of medicinal plants are well-defined by indigenous people of each place worldwide.

Epidemiological and experimental data have demonstrated the significance of aspirin as a revival drug with multiple therapeutic activities such as anti-pyretic and anti-inflammatory action. Other epidemiological studies also revealed the significance of aspirin in cancer biology and its protective role against various types of cancer (Baron, 2003). As aspirin is a well-recognised drug, the willow tree has deeply rooted to profoundly associate with its discovery. This review, therefore, focuses on the historical and philosophical perspectives of aspirin discovery.

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2. The medicinal attributes of the Willow tree to the discovery of aspirin

Traditionally, many ancient civilisations have used herbal remedies to treat various conditions; willow (*Salix* sp.) is one of them (for review see Barrett et al., 1999; Lévesque and Lafont, 2000; Jones, 2001; Cragg and Newman, 2001). The willow tree belongs to the Salicaceae family which includes three species: *Salix alba* L., *Salix pentandra* L. and *Salix purpurea* L. Pharmacologically, the willow exhibits anti-inflammatory, antirheumatic, antipyretic, antidotic, antigesic, and antiseptic properties (Barnes et al., 2002).

The chronological history of the discovery of willow as a medicinal plant can be sorted into three stages: the clinical potential of willow, structural elucidation of the phytotherapeutic salicin, and the chemical synthesis of salicylic acid and aspirin. These are summarised in Table 1. Generally, herbalists have explored nature to assist its survival. Indeed plants have been exploited for food as well as a source of cure for various medical conditions. Early records of using the willow tree, as a source of a medicinal plant, goes back to about 6000 years ago. Indeed, other mammalian species, like monkeys are known to consume plants with medicinal properties (Sumner, 2000). Previous experiences in developing a drug was influenced by the need to prevail over illness and mans experience in seeing the beneficial side of a plant. This concept prevails at present, in combating rare diseases, like cancer. Although it was difficult for ancient people to regulate the dose of herbal medicine to its effective level, failure and success were often expected. Nevertheless, the accumulation of knowledge has profoundly contributed to the development of the norm associated with the concept of herbal medicine as well as to the modern

Table 1 Chronological investigations of willow tree for establishment of aspirin development.

Period	Figure in the field	Clinical/chemical perspective
4000 BC	Assyrians	Used the extract of willow leaves for painful musculoskeletal joint pain conditions as well as antipyretic drug (Jack, 1997; Vane and Botting, 2003)
3500 BC	Sumerian	Described the use of willow leaves for various ailments such as antipyretic drug (Jack, 1997; Vane and Botting, 1998)
1300 BC	Egyptians	Used willow leaves for joint pain and for the relief of pain and inflammation associated with wounds and antipyretic drug (Jack, 1997; Vane and Botting, 1998; Nunn, 1996)
605 BC	Babylonians	Used the willow tree for treatment for fever, pain and inflammation (Chevallier, 1996)
500 BC	Chinese healers	Remedy for various illness (Riddle, 1999)
400 BC	Hippocrates, a Greek Physician	Relieve pain in childbirth and for fever (Riddle, 1999)
0100 AC	Dioscorides, a Greek Physician	Reduce inflammation (De Materia Medica Libri Quinque) (Wells, 2003)
1763	Edward Stone, an Oxfordshire Reverend	Carried the first clinical trial of willow bark and used willow powder to treat ague (Stone, 1763).
1828	Johann Buchner, Professor of Pharmacology, University of Munich	Extracted and purified salicin* from willow bark (Vane and Botting, 1992)
1829	Henri Leroux, a French Pharmacist	Improved the purification process and obtained salicin in crystalline form for the first time (Rainsford, 1984)
1830	Gay-Lussac and Magendie	They showed that salicin was non-nitrogenous compound (Vane and Botting, 1992)
1838	Raffaele Piria, Italian Chemist	Resolved the chemical structure of salicin as a glucosidic salicyl alcohol. Then oxidized salicyl alcohol into salicylic acid (Piria, 1838)
1852	Gerland H.	First to prepare salicylic acid (Gerland, 1852)
1853	Charles von Gerhardt, Professor of Chemistry at Montpellier University	Gave evidence that salicylic acid structure comprises phenol and carboxylic group. He also developed acetylsalicylic acid, or aspirin (Von Gerhardt, 1853; Vane and Botting, 1992)
1859/1860	Hermann Kolbe and E. Lautemann a German Chemists at Marburg University	Discovered the chemical structure of salicyl alcohol and synthesised salicylic acid (Kolbe and Lautemann, 1860)
1874	Hermann Kolbe and E. Lautemann a German Chemists at Marburg University	Industrial scale production of salicylic acid and end of willow powder era use as remedy (Kolbe, 1874)
1876	Thomas MacLagan, a Scottish Physician	Tried willow extract powder on himself before administration of a patient with acute rheumatism (Vane and Botting, 1992)
1893	Felix Hoffman	Synthesised aspirin by acetylating the hydroxyl group of salicylic acid at the ortho position (Sneader, 2000)
1971	Sir John Vane, a British Pharmacologist	He proved the anticoagulant properties of aspirin by blocking the biosynthesis of prostaglandin, the pain messengers. He suggested that aspirin may reduce the risk of cardiovascular disease which led to use low-dose aspirin as a preventative measure in various cardiac conditions (Vane, 1971; Vane and Botting, 1992, 1998)

pharmaceutical concept. Indeed, the modern techniques and methodologies have succeeded to standardise and predict the biological activities of herbal compositions (Kung et al., 2003).

The word salicin is derived from the Latin name for the willow, *salix*. Salicin is a white bitter-tasting powder can be obtained by aqueous extraction of mainly willow bark and leaves. The other names for salicin are: β-*D*-glucopyranoside; 2-(hydroxymethyl)phenyl; 2-(hydroxymethyl)phenyl; 2-(hydroxymethyl)phenyl-β-*D*-glucopyranoside; salicine; salicoside; salicyl alcohol glucoside; and saligenin-β-*D*-glucopyranoside.

Herbalists demonstrated the significance of the willow tree as a medicinal plant to treat patients with various medicinal conditions like fever and pain. The break through in identifying the pharmacological active compound, salicin (the Latin name for the willow), was made by the Italian chemist Raffaele Piria in 1935 (Piria, 1838). He identified the chemical structure of salicin as 2-(hydroxymethyl)phenyl-1-β-*D*-glucopyranoside according to an acid hydrolysis experiment of salicin that claimed to yield pure salicyl alcohol (2-hydroxymethyl phenol) and *D*-glucose moiety (Fig. 1). Salicin also hydrolyzes in the gastrointestinal tract to give *D*-glucose and salicyl alcohol (Fig. 1). Upon absorption, salicyl alcohol is oxidized into salicylic acid and other salicylates compounds such as saligenin, salicyluric acid, salicyl glucuronides, and gentisinic acid which all are eliminated through the kidney (Chrubasik and Shvartzman, 1999; Chrubasik and Eisenberg, 2004). A number of other scientists, like Johann Buchner and Henri Leroux also extracted salicin from willow but was used for clinical trials to treat rheumatism and other related illnesses (Leroux, 1830; Rainsford, 1984; Gross and Greenberg, 1948; Bekemeier, 1977; Vane and Botting, 1992).

The nearest step in elucidating the chemical structure of salicylic acid, the aspirin precursor, was achieved when salicyl alcohol compound was chemically oxidized at the benzyl hydroxyl group to yield salicylic acid. The structure of salicylic acid was identical to an authentic sample, obtained from the oxidation of salicyl aldehyde (Fig. 2). The sample of salicyl

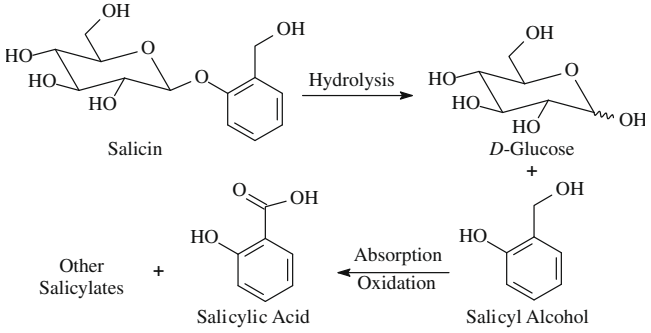

Figure 1 Hydrolysis of salicin.

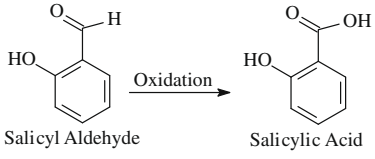

Figure 2 Oxidation of salicyl aldehyde into their acid derivative.

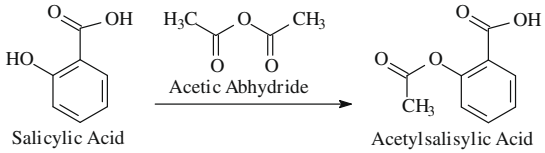

Figure 3 Acetylation of salicylic acid.

aldehyde was also extracted from the meadow sweet flowers (*Filipendula ulmaria*, syn. *Spiraea ulmaria*), by the Swiss pharmacist, Pagenstecher as early as 1835 who passed it to the German chemist, Lowig, for oxidation (Fluckinger, 1888; Rainsford, 1984; Wichtl and Bisset, 1994). *S. ulmaria* flower was also used during the middle ages as analgesic and anti-inflammatory agent. Salicylic acid was then recognised as the pharmacologically active discovery of acetylsalicylic acid, the analgesic drug now commonly known as aspirin (Bradley, 1992; Wichtl and Bisset, 1994).

Salicylic acid was prepared chemically by Kolbe and Lautemann (1860) (Jourdier, 2003; Flieger, 2004), which led to the establishment of large commercial production (the Heyden Chemical Company). However, due to the irritant characteristics of salicylic acid to the upper gastrointestinal tract, which caused Felix Hoffman's father to suffer from the medication of his arthritis, Felix converted salicylic acid into acetylsalicylic acid to reduce this side effect (Fig. 3). Acetylsalicylic acid was then marketed in 1899 under the trademark name aspirin.

The pharmacological properties of aspirin were elaborated in 1960s. Collier (1969a,b) analysed the inhibition effect of some underline cellular mechanism by aspirin and other related drugs. Piper and Vane (1969) discovered the inhibition effect of aspirin on prostaglandin synthesis from archidonic acid, by presenting evidence of a substance called rabbit aorta, which consists mainly of thromboxane A2 and to some extent of the endoperoxides PGG2 and PGH2. Eleven years later, Vane (1971) showed that the synthesis of prostaglandin reduced by salicylate in cell-free homogenates of lung tissue. Vane and Botting (2003) and others (Picot et al., 1994; Loll et al., 1995) illustrated the structure and the mechanism of action of aspirin. It inhibits both cyclooxygenase-1 (Cox-1) and cyclooxygenase-2 (Cox-2) by cross-acetylation of serine moiety at the active site of the enzyme (Higgs and Vane, 1983; Hla and Nelson, 1992; Herschman, 1996). Later, epidemiological studies have led to generate a direct association between aspirin (and other non-esteroidal anti-inflammatory drugs) and cancer risk (Baron, 2003). Aspirin and other salicylates have also shown an effective protective activities against particularly colon cancer (Thun et al., 1991; Funkhouser and Sharp, 1995; Steven, 1995; Rosenberg et al., 1999).

3. The philosophy behind developing herbal willow for therapy

In the last section we looked at the ancient civilisations and how they used natural drugs, such as salicin, in which, until the end of the 1890s, the rationale development of aspirin was archived (Cragg and Newman, 2001). The concept of the long efforts contributed to the discovery of aspirin, has proved the human ability for discovery despite the time and the space. The discovery has often been accomplished by curious explorers of nature. As part of acquiring knowledge they were prompted to fulfil human needs and sustain health. Such talent

proves the possibility of creating an immense stream of knowledge that flows through civilisations where each adds its best flavour. The collective efforts has generated a large bank of information, which has not only led to an understanding of which plant, or certain part of the plant, is more pharmacologically potential, but also led to cultivate the knowledge that have been diversely categorised and documented as edible, toxic, unpalatable, the unpleasant or medicinal (Sumner, 2000).

The willow tree, and many other herbal plants, is the symbol of unseen bridges between nations to harmonise the purity of humanity. The philosophy of herbal medicine was generally pioneered by some figures that undoubtedly used observations and analysis techniques to discover their surrounding. They also used primitive clinical experimentation for investigating the pharmacological effects of plants, which depended upon trial and error process. Each has his own perception towards the interrelationship between plants and human. Although they share the same method which involves searching for rational explanations of events in the natural world. The philosophy of exploring plants for remedies also reveals the concept of association between man and nature, using analogy techniques for investigations. This can be seen in the Reverend Edward Stone challenge in employing the willow bark for the treatment of various ailments. The basic philosophy which drove Reverend Stone to use willow bark as a remedy was his observation that the bitter taste of the willow bark is very similar to peruvian bark (Quinquina, source of quinine) bitterness. This sensational observation made the philosopher, associate the taste property of willow to the therapeutic potential of peruvian bark which was a well-known remedy for paroxysms, fever from agues, malaria and rheumatism (Stone, 1763). His hypothesis for the similarities of the therapeutic action of both barks was tested in a clinical trial study for five years. In his study he used willow bark (*S. alba*) for treatment of paroxysms and fever from agues, or malaria. He concluded that the therapeutic activities of the willow bark which was similar to peruvian bark people used for relevant ailments.

The philosophy of the herbal medicine evolution was also found in ordinary people who were desperately seeking relief for their pain. The discovery of the therapeutic potential of willow tree in England in the middle of the eighteenth century was achieved by an English man who accidentally chewed a twig of willow tree, despite its extraordinary bitter taste; finding himself relieved from his arthritic pain (Sutcliffe and Dunn, 1992). People from different cultures learnt of the therapeutic properties of plants. According to Louis Pasteur's remark, *observation is concerned, chance favours only the prepared mind.* Such a notion may reflect the necessity of humans to survive and the curiosity to discover its surrounding. Humans rely on nature in both health and illness. Archaeological evidence has revealed the considerable knowledge of healing by herbs (Roberts and Manchester, 1995; Pavek et al., 2003). The skills of humans in this respect are tremendous to excel light on the therapeutic basis of various approaches associated with the philosophy of herbal medicine.

The ancients believed that the form, colour and the shape of the plants are closely associated to certain therapeutic virtue. Hence, the *Doctrine of Signatures* by the Neapolitan philosopher, Giambattista della Porta in the Middle Ages, evolved to reflect the thought and the insight of people towards plants. The *Doctrine of Signatures* dictates that the cures for diseases would be found in the same areas where malady occurs. Accordingly, both the willow tree and agues can be found abundantly in moist and wet conditions (Vane and Botting, 1992). This concept had perhaps lead MacLagan to believe further that the association between plant and healing can be extended to include climate: *A remedy for that disease would most hopefully be looked for among those plants and trees whose favorite habitat presented conditions analogous to those under which the rheumatic miasma seemed most to prevail. A low-lying damp locality, with a cold rather than warm climate gives the conditions under which rheumatic fever is most readily produced* (MacLagan, 1876).

The doctoring of signatures also characterizes the medicinal potential of plants according to the visible mark bore in plant that reveal its intended use. White willow (*S. alba*) and quaking aspen (*Populus tremuloids*), for example, were found to be effective for fever, based on the tremulous fluttering of their leaves and branches (Wilkinson, 1997; Barrett et al., 1999). White willow has since been found to contain salicin, and subsequently led to the discovery of aspirin (Wilkinson, 1997). The signatures of many other plants were selected according to their shape characteristics, e.g. heart-shaped leaf as a heart remedy, yellow plant parts for treating hepatitis, etc. The notion of the theory was used in various part of the world, like the Middle East (Lev, 2002), China (Yubin, 2001), Africa and Europe (Stefano and Paracelsus, 1994), despite whether plant bore significant marker relevant to its medicinal use or not.

The main problem associated with the practicality of the *Signature of Doctrine* theory was perhaps, the optimisation of the active ingredients in willow and other plants, which requires analytical techniques, that was not available at that time. Herbalists in the eightieth century started to elucidate the concept of how to optimise dosage of a biologically active substance when it is not chemically pure. The other challenge to the *Doctrine of Signatures* theory was the variation of active substances in medicinal plants, which is influenced by their natural sources, as well as by ecological and environmental conditions. It is clear to ecologists that plant produces salicylic acid in response to pathogens and stress (Raskin, 1992; Hammond-Kosack and Jones, 1996; Ryals et al., 1996; Durner et al., 1997; Wildermuth et al., 2001). Challenges related to the variation of pharmacologically active ingredients in medicinal plants have gradually disappears with the improvement of technology and accumulation of knowledge in medicinal plants.

4. Conclusion

The lessons that have been learnt from the historical perspective of the willow sheds light on the lore of native people and their healers who have exploited their efforts to bring about the wonderful drug, aspirin. Whereas, chemistry has elucidated the chemical structures that lead to the discovery of aspirin.

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