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The historical analysis of aspirin discovery, its relation to the willow tree and antiproliferative and anticancer potential

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Abstract. For several millennia, the willow tree and salicin have been associated with salicylic acid, the key precursor molecule that has contributed to the discovery of acetylsalicylic acid, traded as aspirin. These molecules have been shown to possess phyto- and chemotherapeutic activities as analgesic drugs. In recent decades, aspirin has become the focus of extensive investigation into antiproliferative and anticancer activities. The historical steps that led to the discovery of aspirin, and its antiproliferative and anticancer potential are highlighted in this review.

INTRODUCTION

The willow tree (*Salix* sp.) has achieved a kind of symbolic significance associated with the discovery of aspirin, more than a century ago (Barrett *et al*. 1999; Lévesque & Lafont 2000; Cragg & Newman 2001; Jones 2001), although herbalists and patients have recognized the pharmacological and the clinical potential of not only the willow, but also a variety of other plants (Mayer *et al*. 1949; Lévesque & Lafont 2000; Sumner 2000; Dewick 2002). This comes as no surprise, because medical conditions are as old as our species, and some animals are known to preferentially consume plants with medicinal properties (Sumner 2000).

Analysis of the historical perspective of aspirin discovery starts with clinical investigation during periods before the 18th century, where willow and its extract were used to relieve different types of pain. This century was characterized by advancements in organic chemistry and particularly in pharmaceuticals. This helped to identify the active components of willow when their chemical structures were identified as salicilin, salicylic acid and acetylsalicylic acid; these were subsequently used in a variety of clinical trials. It was not until 1971, however, that the exact pharmacology of aspirin was elucidated when aspirin was shown to interfere with the synthesis of prostaglandins (PGs). Modern epidemiological studies from the 1980s have indicated that aspirin is inversely associated with the risk of developing colorectal cancer. Advances in epidemiological and biological studies have since concentrated on aspirin as a potential anticarcinogenic drug. In addition, aspirin, at relatively high doses (5–20 mM), has been shown to have cell proliferation inhibitory potential in various cancer cell populations. These doses, however, may have diverse effects, and hence limit direct anticancer potential. The main thrust of this review

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is to analyse the historical perspective of willow and its association with the discovery of aspirin and its use in medical/pharmacological fields.

Historical perspective of the discovery of aspirin – attributes of willow

Traditional methods of drug discovery and development have been influenced by the need to prevail over illness and people's experience in witnessing and realizing the beneficial potentials of a plant to cure ailments, perhaps by trial and error (for review see Sumner 2000). The historical account of willow (S*alix* sp.) goes back to early civilizations, particularly in Mesopotamia around 6000 years ago when plants were exploited for food and as a source of drugs.

Experience of both Assyrian (4000 BC) and Babylonian civilizations (605–562 BC) in Iraq has contributed to the development of medicine (Ackerknecht 1973; Sutcliffe & Dunn 1992; Chevallier 1996; Barrett *et al*. 1999; Burns & Fulder 2002). In ancient civilizations of that period, medicine was based on surgeons and physicians using herbal draughts to cure ailments; extracts of the willow tree being used to cure pain and inflammation. Archaeologists have found clay tablets left by the Assyrians from the Sumerian period (3500–2000) describing the use of willow leaves for such conditions (Lévesque & Lafont 2000).

The Babylonians also used willow tree extracts to treat common fever, pain and inflammation. Sumerians were the first known civilization to register medical prescriptions for pain according to a clay tablet from 4000 years ago (Wells 2003). In addition, the Code of Hammurabi (1750 BC), in Mesopotamia, sheds light on a medical history that contributed to the long chain of pharmacological achievements prompted by man's attempt to survive disease. Such notions also prompted Egyptians (1300 BC) to use willow leaves to treat inflammatory conditions. The willow is listed in the herbal remedies in the *Ebers Papyrus* of ancient Egypt (Nunn 1996), which describes the analgesic effects of willow leaves to '*draw the heat out*' of inflamed wounds (Murder 1992; Jack 1997).

Chinese and Greek civilizations also exploited willow bark more than 2000 years ago to alleviate fever and pain (Riddle 1999). The Chinese used poplar tree (*Populus alba* L.) barks and willow (*Salix babylonica* L.) shoots for centuries to treat rheumatic fever, colds, haemorrhages and goitre, and as a general antiseptic for wounds and abcesses (Rainsford 1984). Furthermore, the Greeks also used willow as a form of medicine. The philosopher, Hippocrates (460–370 BC) recommended chewing willow bark to patients suffering from high temperature and pain (Gross & Greenberg 1948; Riddle 1999). He also prescribed a brew of willow leaves to ease the excruciating pains of childbirth. Around 500 years later (100 AD), a further Greek physician, Dioscorides, prescribed willow bark also to reduce the symptoms of inflammation, and the use of willow bark has continued because of its analgesic and anti-inflammatory properties. A further Greek physician, Celsius (1 AD) who treated women with prolapsed uteri with boiled willow leaves and vinegar, is the accepted author of the famed symptoms of inflammation 'redness and swelling with heat and pain'. The Roman Pliny speaks of corns treated with a burned willow bark paste, and Galen treated bloody wounds and ulcers with willow leaves (Wells 2003).

The modern era of aspirin discovery began in the 18th century, when more advanced scientific information had accumulated. In 1763, the Reverend Edward Stone described the beneficial effects of willow bark, in a letter addressed to the Royal Society. Here, Reverand Stone described his results of a clinical study, treating patients suffering from ague (fever, usually taken to be malaria) with powdered willow bark in a dram of water. One hundred and thirteen years later, Thomas MacLagan, a Scottish physician, in 1876 conducted a clinical investigation to test the therapeutic efficiency of willow powder. He successfully treated himself with willow powder extract (salicin) before he applied it to a patient with acute rheumatism. His treatments resulted in a complete reduction of fever and joint inflammation (MacLagan 1876; Sneader 1997). During

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this period, the demand for willow trees increased because of their clinical use. Research into the willow tree in Europe became more focused, especially when supplies of Peruvian bark stopped as a result of the continental blockade imposed by Napoleon at the beginning of the 19th century (Jack 1997).

History of the chemical investigation into the benefits of aspirin

Chemical investigation into the therapeutically active substance in willow extract started in the early 1800s. Wilkinson in 1803 extracted the active substance from *Cortex salicis latifoliae*, which was later found to contain high levels of tannin. In the early 1820s, Brugnateli, and Fontana & Buchner obtained therapeutically active substances of a less contaminated nature and further purification was achieved by Buchner in 1828 at the University of Munich. He removed the tannins and obtained a yellowish substance, which he called *salicin*, the Latin name for the willow. Finally, the pure crystalline form of salicin was obtained by the French pharmacist Henri Leroux in 1829 (Leroux 1830; Rainsford 1984). This was then used for the treatment of rheumatism (Gross & Greenberg 1948; Bekemeier 1977).

A further step forward came with the description of the chemical structure of salicin. Historically, chemical investigations of salicylic acid, the precursor of aspirin, are illustrated in Fig. 1. Gay-Lussac in 1930 indicated that salicin was a non-nitrogenous compound, and in 1935, Raffaele Piria, the Italian chemist found through acid hydrolysis that the salicin structure was comprised of D-glucose and salicyl alcohol moieties (Piria 1838). The salicyl alcohol was then oxidized into salicylic acid where its structure was confirmed with an authentic sample of salicylic acid, obtained from the oxidation of salicylic aldehyde (Fig. 1). Alternatively, the compound has been extracted from meadow sweet flowers (*Spirea ulmaria*) by the Swiss pharmacist, Pagenstecher, in early 1835, who passed it to the German chemist, Lowig, for oxidation that yielded salicylic acid (Fluckinger 1888; Rainsford 1984).

Oxidation of salicyl aldehyde also resulted in the formation of salicylic acid as illustrated. Its structure was further elucidated by the French chemist, Cohours, in 1845 and by the Scottish chemist, Couper, in 1858, who both hydrolysed the methylsalicyl ester in wintergreen (*Gaultheria*) oil upon treatment with phosphorous perchloride (Couper 1858; Geissler & Moller 1889). The hydroxyl radical form readily reacts with the aromatic moiety, which results in hydroxylation. Kolb & Lautemann (Kolb 1860; Kolb & Lautemann 1860) achieved the chemical synthesis of salicylic acid on a small scale. Later, they devised large-scale chemical reactions, which led to the establishment of a commercial establishment, the Heyden Chemical Company, in Germany for the production of salicylic acid for analgesic and antipyretic purposes. However, as salicylic acid was found to be an irritant of the stomach causing bleeding at large doses, salicylic acid was preferentially chemically acetylated by Felix Hoffmann in 1897 to produce acetylsalicylic acid.

Some controversy exists as to who decided to acetylate salicylic acid – Felix Hoffmann or the Heyden Chemical Company. Sneader (2000), Pharmaceutical Historian at the School of Pharmacy, the University of Strathclyde, suggests that the discovery of aspirin should be attributed instead to Arthur Eichengrun, a colleague of Hoffman, who synthesized acetyl salicylic acid as early as April 1897. Eichengrun appears to have been written out of history, perhaps 50 years later by the subsequent Nazi regime who became aware of his Jewish ancestry. Whatever the case, success finally came through when the Bayer Company registered the product under the trade name Aspirin on 6 March 1899 and distributed aspirin to clinics and hospitals for the treatment of patients.

Bayer launched soluble aspirin in the form of tablets in 1900. It soon became known worldwide for safe and effective pain relief. In a few years, aspirin became readily available to doctors and the public and the name *Aspirin* became a drug recognized amongst professionals. It was available to the public in 1915 without prescription.

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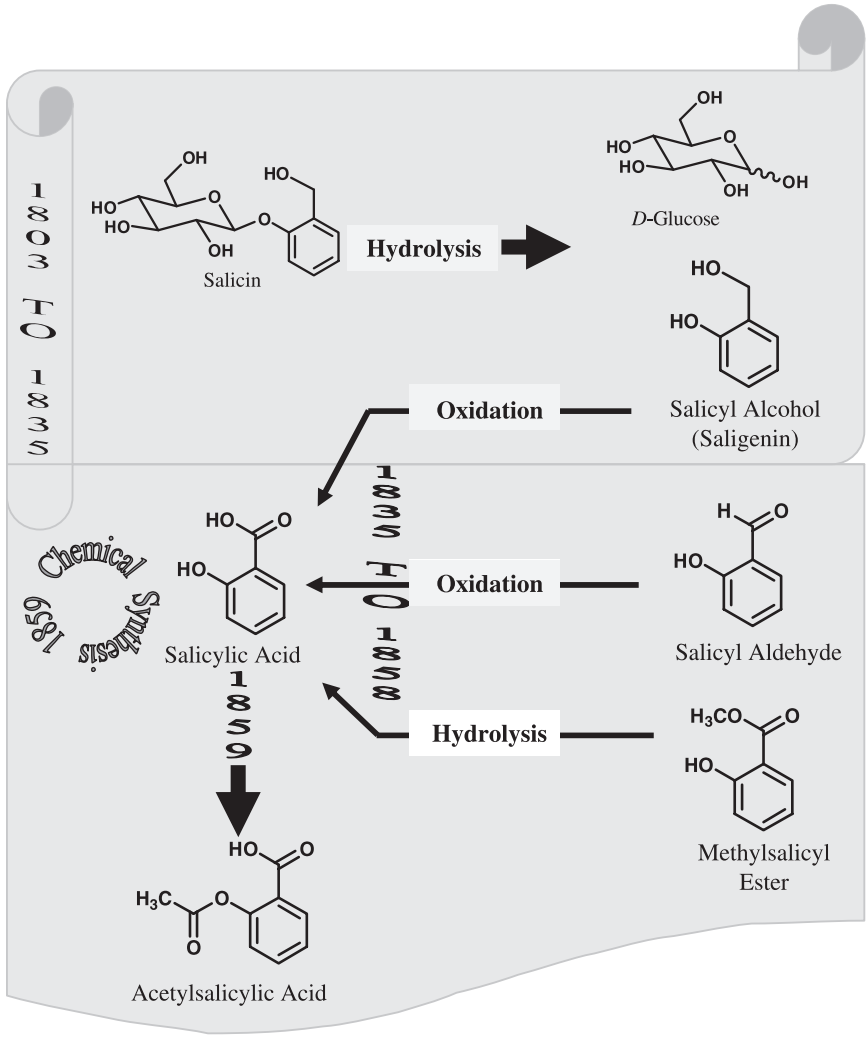

Figure 1. Schematic illustration of the history of aspirin discovery.

Aspirin and its hidden benefits for cancer sufferers

As publicity increased, more clinical and pharmaceutical research was conducted on aspirin, and by the 1920s, therapeutic applications became available for treating symptoms of pain related to rheumatism, lumbago and neuralgia. In 1948, the Californian general practitioner, Lawrence Craven, observed that aspirin taken regularly could dramatically reduce the risk of myocardial infarction (MI). This assumption was based on the fact that none of the 400 patients that were prescribed aspirin suffered heart attacks during the time of the investigation. Such claims have encouraged drug organizations, for example, the US Food and Drug Administration (FDA), to test aspirin as a prophylactic for MI in patients with unstable angina. The FDA also approved the use of aspirin in 1988 for the prevention of recurrent transient ischaemic attacks or *mini-strokes* in men and made aspirin standard therapy for individuals with a history of strokes (Childs 2006).

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Recent epidemiological analyses related to patients on long-term aspirin therapy have indicated a decreased incidence of colorectal cancer (Rodriguez & Huerta-Alvarez 2000; Childs 2006; Rao & Reddy 2004; Zhab *et al*. 2004). These studies indicate that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) protect against colorectal cancer to a greater degree over protection against non-gastrointestinal cancers. Recently, Petersen *et al*. (2005) have shown that a low dose of aspirin protects cells against oxidative damage and induces apoptosis. These features have been shown particularly in human lens epithelial cells, illustrating the evidence of the antioxidant potential of aspirin. Various pieces of evidence suggest that aspirin possesses antiproliferative properties mediated in different cell lines, including human colorectal tumour cells (Bellosillo *et al*. 1998; Din *et al*. 2004), gastric cancer cells (Wong *et al*. 1999), B-cell chronic lymphocytic leukaemia cells (Bellosillo *et al*. 1998), myeloid leukaemia cell lines (Klampfer *et al*. 1999), vascular smooth muscle cells (Marra *et al*. 2000; Brooks *et al*. 2003), colon adenocarcinoma cells (Shiff *et al*. 1996) as well as many other cell types.

Generally, aspirin induces a dose-dependent reduction in the proliferation rate of HT-29 cells (Shiff *et al*. 1996). The sodium salt of aspirin also significantly inhibits cellular proliferation of human pancreatic cancer cell lines (BxPC3 and Panc-1) in a dose-dependent manner (Perugini *et al*. 2000). Goel *et al*. (2003) found similar effects of aspirin on the growth of three different human colon cancer cell populations (HCT116, HCT116 + chr3 and SW480) but at different rates. At 72-h incubation with aspirin treatment, the proliferation rate of HCT116 + chr3 cells was significantly less than inhibition of HCT116 cells at 0.1 mM (14.3% versus 40.7%) and 2.5 mM (27.2% versus 47.9%). All other published investigations have concluded that the inhibitory effects of aspirin on cell population growth and cell proliferation is dose and time dependent (Qiao *et al*. 1998; Wong *et al*. 1999; Zhou *et al*. 2001; Kim *et al*. 2003). Table 1 lists effects of aspirin on the proliferation of different cell lines at different doses and incubation times. Generally, the dose inducing significant antiproliferative and pro-apoptotic effects of aspirin *in vitro* is between 3 mM and 10 mM (Santini *et al*. 1999; Marra & Liao 2001; Zha *et al*. 2004), although in the literature there are reports of higher concentrations of up to 20 mM (Schwenger *et al*. 1997, 1999; Pillinger *et al*. 1998) being effective.

The mechanism by which aspirin and related NSAIDs exert their therapeutic effects in cancer was first established based on the inhibition of PG synthesis. Two isoforms of the enzyme, cyclooxygenase or COX-1 and COX-2, are responsible for the synthesis of PGs in various cells, and these enzymes have been found to play an important role in a number of malignancies (Munkarah *et al*. 2002). PGs are signalling molecules and are responsible for regulating a number of cellular functions, including gene expression, growth and differentiation (Towndrow *et al*. 2000). Many cancers overproduce PGs, and this can be inhibited by aspirin. Aspirin irreversibly

Table 1. The effect of aspirin on cell proliferation and cell population growth

Dose (mM)	Cell line	Max incubation time (h)	Percentage of growth inhibition[a]	Reference
0.4–3	HT-29	73	70–75	Qiao *et al*. (1998)
0.1–10	AGS	72	21–47	Zhou *et al*. (1999)
1	AGS and MKN-28	60	37–40	Zhou *et al*. (2001)
1–5	Ishikawa human endometrial tumour cells	96	21–88%	Arango *et al*. (2001)
1–5	OVCAR-3 ovarian tumour cells	–	Little 68%	Drake & Becker (2002)
1–3	HeLa TG	–	18–55	Kim *et al*. (2003)

[a]Growth inhibition at the highest incubation time, relative to control.

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inhibits both of its isoforms by a cross-acetylation process (Shimokawa & Smith 1992; Lecomte *et al*. 1994; Van & Botting 2003; Wu 2003). Over-expression of COX-2 leads to increased levels of PGs, and hence promotes cellular proliferation, resistance to apoptosis and angiogenesis, processes that contribute to the emergence of the neoplastic phenotype (Husain *et al*. 2001; Munkarah *et al*. 2002; Masmoudi *et al*. 2004). High levels of COX-2 may also confer apoptosis resistance in some cancer cells by activating genes that promote cell survival (Munkarah & Ali-Fehmi 2005; Secchiero *et al*. 2005). Therefore, aspirin may exert its anticarcenogenic properties *via* COX-2 inhibition and subsequently inhibition of PG production, which may result in the induction of apoptosis and/or inhibition of cell proliferation (Husain *et al*. 2001).

In contrast, aspirin can induce antiproliferative effects by non-PG-dependent pathways and affect the progression of the cell cycle (Shiff *et al*. 1996; Arango *et al*. 2001; Stark *et al*. 2001; Goel *et al*. 2003; Gao *et al*. 2004). The effects of aspirin on various cancerous cellular regulatory molecules have been found in the inhibition of NF-κB pathway (Yin *et al*. 1998), $p70^{s6k}$ (Law *et al.* 2000), the Bcl-2 family (Redlak *et al*. 2005), caspases (Belloslo *et al*. 1998; Castano *et al*. 1999; Klampfer *et al*. 1999) and various other intracellular molecules (Pique *et al*. 2000). Aspirin has been shown to prevent H_2O_2-induced activation of NF-κB in a dose-dependent manner through inhibition of phosphorylation and degradation of IκBα and IκBβ in HeLa cells (Kutuk & Basaga 2003). On the other hand, $p70^{s6k}$ is an important member of the MAP kinase signalling family, important for cell cycle progression. Aspirin has been found to inhibit $p70^{s6k}$ activation and phosphorylation in a p38 MAPK-independent manner (Law *et al*. 2000) and Goel *et al*. (2003) have shown that aspirin affects the expression of MMR proteins in colon cancer cell models that are deficient or proficient in a subset of specific genes (for hMLH1, hMLH2, hMLH6 and hMLHS2). These results indicate that the antiproliferative and apoptotic effects of aspirin are mediated by various mechanisms that are cell specific (Han *et al*. 2001).

An appraisal of the development of aspirin

Well before the 19th century, many medicinal plants like willow had become part of the pharmacopeias of allopathy, naturopathy and homeopathy, and their therapeutic basis had been investigated for contemporary approaches by many phytotherapists and physicians. Usually, when a compound is isolated and synthesized, its pharmaceutical uses are more carefully regulated; aspirin, however, has become an early exception (Desmet 1993; Desmet *et al*. 1997; Wells 2003). It is based on a simple molecule with multifunctional groups rendering it capable of various chemical interaction(s) with biological molecules. Hence, it possesses a range of pharmacological activities such as an anti-inflammatory, antirheumatic antipyretic, an antidote, an analgesic, and with antiseptic properties and has become the most common over-the-counter drug. Derivatives and similar common NSAIDs are Ibuprofen, Ketoprofen, Diclofenac Naproxen Meloxicam and Cocodamol; however, aspirin in the last 30 years has become focus on further investigation as a cancer chemopreventive and theapeutic drug. It has been encouraged as the revival of interest in its clinical and pharmacological effects in terms of cancer treatment (Funkhouser & Sharp 1995; Wong *et al*. 1999; Smith *et al*. 2000; Hector *et al*. 2001; Claudia 2003).

Yet, the potential for use of aspirin as an anticancer agent is undermined by the high dose required to show the anticancer potential, and the sensitivity to it of the gastric mucosa. Using a high concentration of aspirin *in vitro* is not comparable with its the commonly prescribed 75 mg (0.04 mM) for human use. Xu *et al*. (1999) indicated that aspirin at 0.01–0.1 mM is the therapeutic concentration that is commonly achieved to selectively inhibit Cox-2 transcription in fibroblasts, and endothelial cells. In contrast, high concentrations used in *in vitro* experiments exhibit nonspecific inhibition of a large number of kinases in cells. Raz (2002) and others (Frantz & O'Neill 1995; Yin *et al*. 1998) have questioned the use of high aspirin doses and

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conclude that its antitumourogenic effect *in vivo* is the result of the inhibition of tumour cell Cox-2. Also, Wang & Dubois (2005) have reported that prolonged use of high doses of Cox-2 inhibition leads to serious cardiovascular side –effects. This mechanism, though, may not have substantial relevance to the one that mediates the effects of NSAIDs *in vitro*, because of high concentrations habitually used in *in vitro* experiments (Raz 2002). Furthermore, it has been reported recently that high aspirin concentration used in cancer treatment causes complications to heart function (Patrono *et al*. 2004). Further investigations are therefore recommended using more physiological doses to weigh against the cost/benefit ratio of aspirin therapy in cancer (Mahdi *et al*. 2005).

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