

# Anticancer prospection of salicin, a historical origin of aspirin

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## Abstract

Salicin (an alcoholic  $\beta$ -glucoside), the historical origin of aspirin. It is chemically related to aspirin and tastes bitter like quinine and evident for a number of important biological activities. The human bitter taste receptor TAS2R16 (hTAS2R16) responds to  $\beta$ -glucosides such as salicin. Thus, a modulator effect on this receptor may link to salicin-induced anticancer effect. Moreover, it may act by reducing oxidative stress and inflammatory reactions. Among a number of anticancer cellular and molecular mechanisms, salicin is evident to act through suppressing the angiogenic activity in cancer cells. Salicin may be one of the important anticancer drugs. However, the research on this willow plant derived compound is not sufficient, especially in the context of anticancer drug investigation.

**Keywords:** Cancer; Chemoprevention; Salicin.

## 1. Introduction

Salicin (Figure 1), an alcoholic  $\beta$ -glucoside is produced in (and named after) willow (*Salix*) barked. It is also found under the bark of *Populus* spp. and castoreum. Evidence suggests that it has anti-bacterial (Thomason et al., 2004), pain, headache (Wölfle et al., 2015), anti-inflammatory (Rudeekulthamrong and Kaulpi boon, 2016), analgesic, antipyretic (Pincock, 2005), thrombolytic (Jedinák et al., 2006), and neuro protective activity (Yang et al., 2013). It is structurally similar to aspirin and restricted to the patients having asthma, diabetes, gout, gastritis, hemophilia, stomach ulcers as well as children under 16, and pregnant and breast-feeding women.

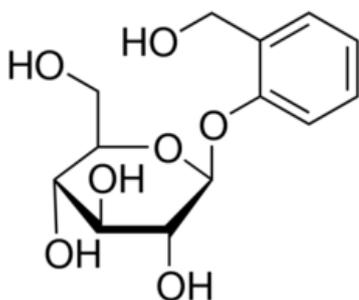


Fig. 1: Salicin [2-(Hydroxymethyl) Phenyl-B-D-Glucopyranoside].

Cancer, a disorder of cell proliferation may lead to tumor production, and it is still an uncontrolled disease and a major cause of death worldwide. Chemotherapy, among the others is a popular therapeutic approach to cancer treatment. Findings on willow tree (*Salix* spp.), especially on salicin suggest that it can be used for the treatment and prevention of cancer. This writing aims to sketch a current scenario of anticancer potential of salicin.

## 2. Anticancer aspects of salicin

The crude water extracts of the young leaves of *S. safsaf* exerted a cytotoxic effect on the acute myeloid leukemia (El-Shemy et al., 2003). This extract was also evident to act against human carcinoma cells (*in vivo* and *in vitro*). The authors suggested possible mechanisms may include – apoptotic cell death, DNA damage, and cell membrane rupture and/or protein denaturation (El-Shemy et al., 2007). In a study, salicin isolated from the willow bark extracts inhibited the cell growth and promotes apoptosis in human colon (HT 29 and HCT 116) and lung cancer (A 549 and SW2) cell lines, irrespective of their cyclooxygenase (COX)-selectivity (Hostanska et al., 2007). However, the water extract of willow bark also showed an anti-proliferative effect on colon-carcinoma cell line HT-29, where an increased COX-1 and COX-2 mRNA expressions was also observed (Bonaterra et al., 2010).

Inflammation frequently accompanies the progress of cancer, especially the colorectal cancer (CRC). In a study, the ethanolic extract of the *S. aegyptiaca* (a *Salix* species), which was rich in salicin, catechin. Catechol strongly reduced the proliferation of HCT-116 and HT29 CRC cells, possibly *via* cell cycle arrest at G1/S independent of DNA damage, induction of apoptosis through a p53 dependent pathway and an inhibition of phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) pathways (Enayat et al., 2013). The ethanolic extract was also evident to amplify apoptosis of neoplastic cells within the colon mucosa of the 1, 2-dimethyl hydrazine (DMH)-treated mice along with the lowering of the levels of epidermal growth factor receptor (EGFR), nuclear  $\beta$ -catenin, and COX-2 in colon cancer cell lines HT-29 and HCT-116, suggesting a potential source of the chemo preventive agent (Bounaama et al., 2016).

The extract of Willow's bark is also evident to exert an antioxidative effect in the human umbilical vein endothelial cells (HU-VECs) and *Caenorhabditis elegans* (Ishikado et al., 2013), where the extract prevented oxidative-stress-induced cytotoxicity by

increasing mRNA and protein expression levels of the nuclear factor erythroid 2-related factor 2 (Nrf2) target genes heme oxygenase-1,  $\gamma$ -glutamylcysteine ligase modifier and catalytic subunits, and p62 and intracellular glutathione (GSH) in HUVECs, gcs-1::green fluorescent protein reporter (a target of the Nrf2 ortholog SKN-1) in HUVECs and death of *C. elegans*. In another study, salicin induced in SH-SY5Y cells phosphorylation of extracellular-signal-regulated kinase (ERK) and cyclic AMP-responsive element-binding protein 1 (CREB), the key transcription factors of neuronal differentiation, suggesting a modulatory effect on neurite outgrowth by bitter taste receptor activation (Wölfle et al., 2015). Salicin derivatives, namely saliglandin and 6'-O-(Z)-p-coumaroylsalicin 14 another fourteen analogues isolated from the twigs of *S. glandulosa* decreased nitric oxide (NO) synthesis in lipopolysaccharide (LPS)-activated microglial cell (BV-2). Moreover, one of them was found to increase the nerve growth factor (NGF) production in C6 glioma cells, suggesting the salicin derivatives having potent anti-neuroinflammatory effects (Kim et al., 2015).

Salicin is evident to exert an anticancer effect on Ehrlich's ascites carcinoma (EAC) (*in vivo*), human breast cancer (MCF7 cell line, *in vitro*) and the pancreatic cancer cell line (Panc-1, *in vitro*) by decreasing in tumor weight, tumor volume, the carcinoembryonic antigen (CEA) level, and reduced tumor cholesterol content through an antioxidant (reduced malondialdehyde level and increased GSH and catalase content) and an anti-inflammatory activity (reduced tumor necrosis factor alpha (TNF- $\alpha$ ) level) *in vivo*, while activation of caspase 3/7 apoptotic pathway in *in vitro* models (Sabaa et al., 2017).

Angiogenesis is an essential process for tumor progression, thus, negative regulation of this process may be a helpful strategy for antitumor therapy. In a study, salicin was found to suppress the angiogenic activity on endothelial cells, such as migration, tube formation, and sprouting from an aorta. Additionally, it reduced reactive oxygen species (ROS) production and activation of the extracellular signal-regulated kinase pathway (Kong et al., 2014).

### 3. Conclusion

In summary, the antioxidant and anti-inflammatory activities, especially the ROS scavenging and induction capability of physiological antioxidants in the first case, while inhibitory of pro-and/or inflammatory mediators in the second case may link with its anticancer potential. Moreover, salicin can act through the bitter taste receptor as well as a number cellular and molecular pathways as an anticancer candidate. Salicin as well as the willow bark may be one of the potential sources of anticancer drugs. More research is required on salicin's anticancer effects.

### 4. Conflicts of interest

None declared.

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