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REVIEW

Efficacy and Safety of White Willow Bark (*Salix alba*) Extracts

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Willow bark extract has been used for thousands of years as an anti-inflammatory, antipyretic, and analgesic. In spite of its long history of use, relatively few human and animal studies have been published that confirm anecdotal observations. A small number of clinical studies have been conducted that support the use of willow bark extracts in chronic lower back and joint pain and osteoarthritis. Willow bark extracts also are widely used in sports performance and weight loss products presumably because of anti-inflammatory and analgesic activities, although no human studies have been published that specifically and directly document beneficial effects. In recent years, various *in vitro* and animal studies have demonstrated that the anti-inflammatory activity of willow bark extract is associated with down regulation of the inflammatory mediators tumor necrosis factor-α and nuclear factor-kappa B. Although willow bark extracts are generally standardized to salicin, other ingredients in the extracts including other salicylates as well as polyphenols, and flavonoids may also play prominent roles in the therapeutic actions. Adverse effects appear to be minimal as compared to non-steroidal anti-inflammatory drugs including aspirin. The primary cause for concern may relate to allergic reactions in salicylate-sensitive individuals.

Keywords: Willow bark extract; *Salix alba*; anti-inflammatory; analgesic; osteoarthritis; lower back pain; sports performance; weight loss.

INTRODUCTION

White willow bark extract is an extract of the white bark of *Salix alba* that is standardized for its salicin content. Various grades of the extract are commercially available and contain, for example, 15%, 25%, or 50% salicin. Historically, willow bark has been used for over 2000 years, initially in the Mediterranean region including Egypt and Greece and subsequently in China, Europe, North America, South America, and Caribbean. Use of willow bark extract to treat pain and fever was reported in 1763 in England (Highfield and Kemper, 1999).

White willow bark extract is widely used for conditions associated with pain, inflammation, or fever such as joint or knee pain, acute back pain, osteoarthritis, headache, menstrual cramps, tendonitis, flu symptoms including fever, and generalized pain (Highfield and Kemper, 1999). A limited number of clinical studies have been conducted with willow bark extract, and these as well as animal and mechanistic *in vitro* studies will be summarized in the succeeding sections.

CHEMISTRY

The previously listed properties of willow bark extract are believed to be associated at least in part with its salicin content, which is a salicylate glycoside (Fig. 1). An HPLC mass spectrometry analysis of aqueous extracts of willow bark have shown the presence of at least 11 related salicylate compounds including salicin, saligenin, salicylic acid, isosalicin, salidroside, picein, triandrin, salicoylsalicin, salicortin, isosalipurpuroside, and salipurpuroside (Kammerer *et al.*, 2005). The composite of these related constituents may be responsible for the anti-inflammatory, analgesic, and antipyretic effects that are generally attributed to salicin.

Upon ingestion, more than 80% of salicin present in willow bark extract is absorbed (Steinegger and Hovel, 1972). Salicin and salicortin, the two most prominent salicylates in willow bark extract, are metabolized by the intestinal flora to saligenin, which is absorbed and metabolized by the liver to salicylic acid (Julkunen-Tiitto and Maeier, 1992; Fotsch *et al.*, 1989). Salicin and salicylic acid were widely used in the 19th century as analgesics and antipyretics (Highfield and Kemper, 1999).

Of interest is the fact that the salicin and the salicin-related content of willow bark extract cannot fully explain its clinical efficacy (Nahrstedt *et al.*, 2007). In addition to the salicin-related constituents, various polyphenolics and flavonoids are also present (Kammerer *et al.*, 2005; Nahrstedt *et al.*, 2007). Agnolet *et al.* (2012) conducted a comprehensive analysis of willow bark products and identified 16 compounds in commercial willow bark extracts. In addition to salicin and salicin derivatives, catechin, amelopsin, taxifolin, 7-O-methyltaxifolin-3'-O-glucoside, and 7-O-methyltaxifolin were identified. Compounds such as catechin and amelopsin are known to possess high antioxidant and free radical scavenging activity, and these other constituents in white willow bark may exhibit

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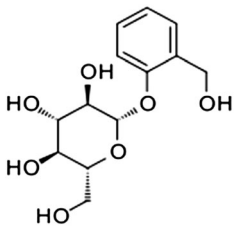

Figure 1. Salicin.

antioxidant, antiseptic, and immune-enhancing properties (Highfield and Kemper, 1999). This complex mixture of ingredients may explain why the typical dose of willow bark extract is in the range of 120–240 mg salicin as compared with a typical dose of 500 mg for aspirin (acetylsalicylic acid).

HUMAN CLINICAL STUDIES

Pain and inflammation management

Vlachojannis *et al.* (2009) conducted a systematic review of the effectiveness of willow bark extract on musculoskeletal pain. These authors concluded that ethanolic extracts of willow bark were effective in treating low back pain. Three clinical studies were included in this review that examined the utility of willow bark extract in pain management involving a total of 415 subjects. The three studies involved in this review are described in the succeeding paragraphs.

Chrubasik *et al.* (2000) examined the ability of willow bark extract to relieve chronic low back pain. They enrolled 210 patients who were randomized to placebo, 120 mg or 240 mg salicin in a 4-week trial. The number of patients that were pain free in the last week of treatment was 39% for the high dose, 21% for the low dose, and 6% for the placebo. The response in the high dose of willow bark extract was evident after 1 week of treatment. One patient suffered a severe allergic reaction.

Schmidt *et al.* (2001) conducted a randomized placebo-controlled, double-blind study involving 78 patients with osteoarthritis. The subjects received the placebo or 240 mg salicin per day for 2 weeks. A moderate, statistically significant decrease (14%) in the western Ontario - McMaster University osteoarthritis (WOMAC) pain score was observed in the treated group relative to baseline. The willow bark was well tolerated with no adverse effects reported.

In a study by Biegert *et al.* (2004), 127 patients with osteoarthritis and 26 patients with rheumatoid arthritis were treated with 240 mg salicin per day for 6 weeks. Based on the WOMAC score, no significance was shown with respect to pain relief in either group receiving the salicin. No verification that the extract contained 240 mg salicin was provided, and no adverse effects were reported. The reason for the lack of effect of willow bark extract relative to the two previous studies (Chrubasik *et al.*, 2000; Schmidt *et al.*, 2001) is unclear, and no explanation was provided by the authors.

Two more recent clinical studies have been published and were not included in the review of Vlachojannis *et al.* (2009). In a 6-month study by Uehleke *et al.* (2013), 436 patients with rheumatic pain due to osteoarthritis or back pain or a combination of both were included using mono or combination therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. The product used was an aqueous willow bark extract (STW 33–1; Proaktiv®, Des Moines, IA USA). The authors reported that pain scores were between 33% and 44% of baseline in conjunction with the use of the willow bark extract. No relevant drug interactions were reported.

An 8-week placebo-controlled, double-blind study was conducted by Nieman *et al.* (2013) involving 100 subjects between the ages of 50–75 years with a history of joint pain. The subjects consumed three capsules per day of a commercial product (Instaflex™ Joint Support, Charlotte NC USA) or placebo. In addition to 250 mg white willow bark extract (15% salicin), the commercial product contained in three capsules glucosamine sulfate, methylsulfonylmethane, ginger root concentrate, *Boswellia seratta* extract (65% boswellic acid), turmeric root extract, cayenne, and hyaluronic acid. The results demonstrated that the treated group exhibited significant reductions in joint pain (37% vs. 16%) and joint stiffness (30% vs. 12%) relative to the placebo group. Significant improvement in ability to perform daily activities was also reported. However, it is not possible to determine the contribution of white willow bark extract to these beneficial effects because of the complex nature of the product.

Based on a summary of these studies in conjunction with its anecdotal use for hundreds of years, the results indicate that willow bark extract is effective as an analgesic and anti-inflammatory.

Weight loss and sports performance

Willow bark extract and salicylates are also used extensively in weight loss and weight management products as well as in sports performance products (Armstrong *et al.*, 2001). However, a paucity of well-controlled studies has been published assessing the specific effects of willow bark extract and salicin on weight loss or sports performance. Their beneficial effects may be due to an increase in pain tolerance as well as antioxidant and anti-inflammatory properties because obesity and intense exercise involve inflammatory processes and in addition, pain relief increases mobility, exercise performance, and energy consumption. Furthermore, if a person is feeling better as a result of using willow bark extract, that individual may be more likely to follow their dietary goals and exercise at a higher performance level.

In a study by Hudson *et al.* (2008) involving weight (resistance) training, the administration of acetylsalicylic acid (10 mg/kg) was shown to significantly decrease perceived pain index and increase resistance training performance. This effect is believed to occur through the modulation of cyclooxygenase-2 (COX-2), prostacyclins, and interleukins (Bogar *et al.*, 1995; Buford *et al.*, 2009). Although this study was not conducted with white willow bark extract and salicin, it does demonstrate that salicylates may exhibit beneficial effects with respect to sports performance.

Similarly, Mauger *et al.* (2010), using performance during time trial cycling, have shown that the use of a non-steroidal anti-inflammatory agent (acetaminophen) enabled participants to cycle at a higher power output without a change in perceived pain or exertion. Their observations support the contention that exercise is

regulated at least in part by pain perception, and increasing pain tolerance can improve the capacity for exercise.

Studies have been reported on the use of combination products containing salicin or white willow bark extract with respect to weight loss and sports performance (Kalman *et al*., 2000; Armstrong *et al*., 2001; Boullata *et al*., 2003; Haller *et al*., 2008). The products used in these studies also contained ingredients such as extracts of green tea, yerba mate, ginger, bitter orange, kola nut, and grape seed. However, in no case was the specific effect or contribution of the salicin or willow bark extract determined relative to the other components of the products.

ANIMAL STUDIES

In a study involving obese mice, Yuan *et al*. (2001) demonstrated that salicylates were able to reverse obesity and diet-induced insulin resistance, implicating inflammatory processes in the pathogenesis of insulin resistance and obesity. As a consequence, various commercial thermogenic weight loss supplements contain willow bark extract (Armstrong *et al*., 2001).

In a study involving rats, the animals were treated for 14 days with a standardized willow bark extract or various isolated fractions at a dose of 30 mg/kg (Ulrich-Merzenich *et al*., 2012). The results showed that the willow bark extract and the salicyl alcohol-rich fraction were able to decrease the forced swimming test induced immobility time by 36–44%. Analysis of whole rat genome microarray indicated that both inflammatory (interleukin) and neurological (serotonin) targets were involved in the modulation of the forced swimming test by willow bark extract and the salicyl alcohol fraction.

In a study involving streptozotocin-induced diabetes in rats, the animals were treated daily by injection with a fortified extract suspension of 150 mg/kg white willow bark extract (15% salicin) in combination with *Ginkgo biloba* extract, α-lipoic acid, a red berry extract, and L-carnosine for 10 days (Bucolo *et al*., 2013). The fortified extract was shown to attenuate diabetes-induced plasma lipid peroxidation by 50%. Furthermore, the fortified extract attenuated the diabetes-induced retinal inflammation as determined by significant decreases in retinal tumor necrosis factor-α (TNF-α) and vascular epidermal growth factor levels. Again, the precise role of the white willow bark extract with respect to the anti-inflammatory and antioxidant properties of this combination product is not known.

IN VITRO MECHANISTIC STUDIES

In recent years, a number of *in vitro* studies have assessed the mechanism(s) of action of willow bark extracts and fractions isolated therefrom. As a consequence, significant insight into the anti-inflammatory and analgesic activities of willow bark extract has been obtained.

Bonaterra *et al*. (2010) examined the anti-inflammatory effects of a commercial willow bark extract (STW 33-I; Proaktiv®) in lipopolysaccharide-activated human monocytes and differentiated macrophages in comparison with the NSAIDs aspirin (acetylsalicylic acid) and diclofenac. This *in vitro* investigation indicated that the willow bark extract as well as a water soluble fraction exhibited significant anti-inflammatory activity by inhibiting pro-inflammatory cytokines as TNF-α, COX-2, and nuclear translocation of the transcription factor nuclear factor-kappa B (NF-κB) in activated monocytes.

In a subsequent study involving the commercial willow bark extract (STW 33–1), the activity of the extract and various fractions thereof were tested for their ability to inhibit TNF-α-induced expression of intracellular adhesion molecule-1, a measure of anti-inflammatory activity, in human microvascular endothelial cells (Freischmidt *et al*., 2012). The authors concluded that not only salicin derivatives but also catechin and flavonoids did contribute to the anti-inflammatory activity of the willow bark extract.

Ishikado *et al*. (2012) also showed that a salicin free extract of willow bark induced antioxidant enzymes and prevented oxidative stress through activation of nuclear factor erythroid-2 related factor-2 in human umbilical vein endothelial cells and the nematode *Caenorhabditis elegans*. These studies provided additional information regarding the mechanism of action of willow bark extract and demonstrated activities beyond salicin derivatives.

Shakibaei *et al*. (2012) conducted a study designed to characterize the anti-inflammatory mode of action of various plant extracts. With respect to willow bark extract, the extract was shown to exhibit anti-inflammatory and anabolic effects on canine articular chondrocytes. The extract reversed interleukin-1β induced NF-κB activation through a complex mechanism involving down regulation of COX-2 and matrix metalloproteinases.

An aqueous extract of willow bark was shown to exhibit greater anti-inflammatory activity through reducing interleukin-6 and TNF-α production than apigenin, quercetin, and salicylic acid in human acute monocytic leukemia cell line macrophages (Drummond *et al*., 2013). Furthermore, isolated salicylic acid was shown to protect against oxidative DNA damage in these cells.

Coffee extracts and caffeine are commonly used in conjunction with willow bark extract, and a study of the interactions between active constituents of coffee and willow bark extract was conducted (Durak and Gawlik-Dziki, 2014). Synergism was observed between the phenolic constituents of these two sources with respect to the ability to inhibit lipid peroxidation and reducing power. However, antagonism was observed with respect to scavenging 2,2'-azino-bis (ethylbenzothiazoline-6-sulfonic acid) (ABTS) cation radical. The reason for these opposing effects was not elucidated.

Several studies have examined the antineoplastic activity of willow. In one study, willow bark extract (BNO 1455) and various fractions thereof were shown to suppress growth and induce apoptosis (programmed cell death) in human colon and lung cancer cells *in vitro* (Hostanska *et al*., 2007). The salicin-related, flavonoid, and proanthocyanidin fractions all exhibited anti-proliferative activity.

In another study, the antineoplastic activity of an aqueous extract of willow leaves was examined against three different carcinoma cells *in vivo* and *in vitro* (El-Shemy *et al*., 2007). The oral administration of the willow extract was shown to prolong life and reduce

tumor growth when Ehrlich ascites carcinoma cells were injected intraperitoneally in mice. *In vitro*, the extract killed 75–80% of acute lymphoblastic leukemia and acute myeloid leukemia cells harvested from human patients. The constituents responsible for these effects were not identified.

The earlier studies provide extensive data regarding the anti-inflammatory and antioxidant activities of willow bark extracts. The down regulation of various inflammatory factors as TNF-α, COX-2, and NF-κB are documented. Not only the role for salicin and related derivatives has been demonstrated but also the involvement of polyphenolics as catechins and flavonoids has also been indicated.

SAFETY

As previously noted, salicin is chemically related to salicylic acid and aspirin (acetylsalicylic acid). However, salicin does not appear to be as irritating to the stomach as either salicylic acid or aspirin, and as a consequence, side effects tend to be mild (Highfield and Kemper, 1999).

People who are allergic to aspirin should avoid using white willow bark (Steinegger and Hovel, 1972; Schmidt *et al*., 2001). A case study involving an anaphylactic reaction has been reported in which the subject had a known allergy to aspirin (acetylsalicylic acid) and took two capsules of Stacker 2, (NVE Pharmaceuticals, Andover, NJ USA) which contained willow bark extract (Boullata *et al*., 2003). Treatment with epinephrine, diphenhydramine, and a corticosteroid were required. No challenge test was conducted to confirm that willow bark was directly involved.

The clinical study of Chrubasik *et al*. (2000) also reported one case of a severe allergic reaction to a willow bark extract in the absence of other ingredients. A report of acute respiratory distress syndrome presumably because of white willow bark extract was recently reported (Srivali *et al*., 2013). The patient suddenly developed shortness of breath and a non-productive cough 30 min after ingesting a white willow bark supplement. No information was provided regarding the source or composition of the supplement, and no challenge test was performed to verify the cause. The patient was successfully treated with methylprednisolone, diphenhydramine, and ranitidine.

Various cautionary statements and warnings have been issued regarding the use of willow bark extract (Anon, 2011). It has been suggested that people with gastritis, stomach ulcers, diabetes, asthma, or hemophilia should avoid willow bark extract. Furthermore, it has been noted that willow bark may interact with anticoagulants (increase the risk of bleeding), beta blockers and diuretics (decrease the effect of the drugs), and NSAIDs (increase the risk of stomach bleeding) (Anon, 2011). In addition, children under the age of 16 years should not use white willow bark extract because of the potential for causing Reye syndrome.

Although the earlier interactions and effects are theoretically possible and in spite of the wide spread use of willow bark extract, no cases of stomach ulcers, bleeding disorders, or drug interactions have been reported. Again, the most serious adverse effect has been putative anaphylactic reactions in individuals allergic to aspirin and salicylates in general (Steinegger and Hovel, 1972; Chrubasik *et al*., 2000; Schmidt *et al*., 2001; Boullata *et al*., 2003; Srivali *et al*., 2013). A study of 70 products containing willow bark extract alone or with other ingredients found that only 4.3% listed a warning about aspirin sensitivity and 2.9% listed a warning about Reye syndrome (Clauson *et al*., 2005).

SUMMARY AND CONCLUSIONS

Although willow bark preparations have been used for many years for their analgesic and anti-inflammatory properties, relatively few published studies exist verifying anecdotal observations. A total of five human clinical studies and several animal studies have been conducted. In general, the results of these studies support the use of willow bark extracts for their analgesic and anti-inflammatory activity. No direct evidence exists for the use of willow bark extract in weight loss and sports performance products, although several studies involving combination products have reported positive results. The argument can be made that obesity and sports-related exertion involve inflammatory processes.

The typical dose of 120–240 mg salicin in the form of willow bark extract is lower than a typical dose of aspirin (500 mg). This difference may be due to the presence of polyphenols and flavonoids present in the extract, which exert beneficial effects.

In recent years, a series of *in vitro* studies have assessed the mechanisms of action of willow bark extracts and fractions that have been isolated therefrom. The data from these studies are generally consistent with knowledge regarding anti-inflammatory and analgesic mechanisms. The results of these studies have demonstrated that down regulation of the pro-inflammatory effects of TNF-α, COX-2, and NF-κB occurs in response to willow bark extracts.

With respect to safety, rare allergic reactions constitute the primary caution and concern. Individuals with a known history of allergic reactions to salicylates should avoid willow bark extracts. Although several drug interactions and risk of ulcers and bleeding are theoretically possible, no documented and reported cases exist. A possible reason for the lack of these effects may again be due to the presence of constituents in addition to salicin-like compounds within willow bark extracts which act as antioxidants and tissue protectants. The antioxidant and free radical scavenging properties of various polyphenols and flavonoids present in willow bark extracts as catechin and amelopsin are well known. However, this possibility has yet to be specifically or conclusively demonstrated.

In summary, although willow bark extract have been used for many years, the number of human and animal studies addressing its safety and efficacy is limited. A much larger number of studies have examined the mechanisms associated with the anti-inflammatory and analgesic actions of willow bark extract and salicin, and these studies lend support to the continued use of these products.

Conflict of Interest

The authors have declared that there is no conflict of interest.

REFERENCES

Agnolet S, Weise S, Verpoorte R, Staerk D. 2012. Comprehensive analysis of commercial willow bark extracts by new technology platform: combined use of metabolomics, high-performance liquid chromatography-solid-phase extraction-nuclear magnetic resonance spectroscopy and high-resolution radical scavenging assay. *J Chromatog A* **1262**: 130–137.

Anon. 2011. Willow bark. U. Maryland Med. Center, pp 1–6. Http://www.umm.edu/altmed/articles/willow-bark-000281.htm.

Armstrong WJ, Johnson, P, Duhme, S. 2001. The effect of a commercial thermogenic weight loss supplement on body composition and energy expenditure in obese adults. *J Exer Physiol* (on line) **4**: 28–35.

Biegert C, Wagner I, Ludke R, *et al.* 2004. Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid arthritis: results of 2 randomized double-blind controlled trials. *J Rheumatol* **31**: 2121–2130.

Bogar RH, Bode-Bogar SM, Shroder EP, Tsikas D, Frolich JC. 1995. Increased prostacyclin production during exercise in untrained and trained men: effect of low-dose aspirin. *J Appl Physiol* **78**: 1832–1838.

Bonaterra GA, Heinich EU, Kelber O, Weiser D, Metz J, Kinscherf R. 2010. Anti-inflammatory effects of the willow bark extract STW 33-I (Proaktiv®) in LPS-activated human monocytes and differentiated macrophages. *Phytomed* **17**: 1106–1113.

Boullata JI, McDonnell PJ, Oliva CD. 2003. Anaphylactic reaction to a dietary supplement containing willow bark. *Ann Pharmacother* **37**: 832–835.

Bucolo C, Marrazzo G, Platania CBM, Drago F, Leggio GM, Salmone S. 2013. Fortified extract of red berry, *Ginkgo biloba*, and white willow bark extract in experimental early diabetic retinopathy. *J Diabetes Res* . DOI:10.1155/2013/432695.

Buford TW, Cooke MB, Shelmadine BD, Hudson GM, Redd L, Willoughby DS. 2009. Effects of eccentric treadmill exercise on inflammatory gene expression in human skeletal muscle. *Appl Physiol Nutr Metab* **34**: 745–753.

Chrubasik S, Eisenberg E, Balan E, Weinberger T, Luzzati R, Conradt C. 2000. Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. *Am J Med* **109**: 9–14.

Clauson KA, Santamarina ML, Buettner CM, Cauffield JS. 2005. Evaluation of presence of aspirin-related warnings with willow bark. *Ann Pharmacother* **39**: 1234–1237.

Drummond EM, Harbourne N, Marete E, *et al.* 2013. Inhibition of pro-inflammatory biomarkers in THP1 macrophages by polyphenols derived from chamomile, meadowsweet and willow bark. *Phytother Res* **27**: 588–594.

Durak A, Gawlik-Dziki U. 2014. The study of interactions between active compounds of coffee and willow (*Salix* sp.) bark water extract. *Biomed Res Int* . DOI:10.1155/2014/386953.

El-Shemy HA, Aboul-Enein AM, Aboul-Enein KM, Fujita K. 2007. Willow leaves extracts contain anti-tumor agents effective against three cell types. *PLoS One* Jan. 31, **2**(1): 1–10. http://www.plosone/org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0000178.

Fotsch G, Pfeifer S, Bartoszek M, Franke P, Hiller K. 1989. Biotransformation of phenolglycosides leiocarposide and salicin. *Pharmazie* **44**: 555–558.

Freischmidt A, Jurgenliemk G, Kraus B, *et al.* 2012. Contribution of flavonoids and catecholto the reduction in ICAM0-1 expression in endothelial cells by standardized willow bark extract. *Phytomed* **19**: 245–252.

Haller CA, Duan M, Jacob P III, Benowitz N. 2008. Human pharmacology of a performance-enhancing dietary supplement under resting and exercise conditions. *Br J Clin Pharmacol* **65**: 833–840.

Highfield ES, Kemper KJ. 1999. White willow bark (*Salix alba*). *The Longwood Herbal Task Force*, 1–12. http://www.mcp.edu/herbal/default.htm.

Hostanska K, Jurgenliemk G, Abel G, Nahrstadt A, Saller R. 2007. Willow bark extract (BNO1455) and its fractions suppress growth and induce apoptosis in human colon and lung cancer cells. *Cancer Detect Prev* **31**: 129–139.

Hudson GM, Matt GJ, Bishop PA, Richardson MT. 2008. Effects of caffeine and aspirin on light resistance training performance, perceived exertion, and pain perception. *J Stren Condit Res* **22**: 1950–1957.

Ishikado A, Sono Y, Matsumoto M, *et al.* 2012. Willow bark extract increases antioxidant exzymes and reduces oxidative stress through activation of Nrf2 in vascular endothelial cells and *Caenorhabditis elegans*. *Free Rad Biol Med*. DOI:10:1016/j.freeradbiolmed.2012.12-006.

Julkunen-Tiitto R, Maeier B. 1992. The enzymatic decomposition of salicin and its derivatives obtained from Salicaceae species. *J Nat Prod* **55**: 1204–1212.

Kalman DS, Colker CM, Shu Q, Swain MA. 2000. Effects of a weight-loss aid in healthy overweight adults: double-blinded, placebo-controlled, clinical study. *Curr Ther Res* **61**: 199–205.

Kammerer B, Kahlich R, Bieger C, Gleiter CH, Heide L. 2005. HPLC-MS/MS analysis of willow bark extracts contained in pharmaceutical preparations. *Phytochem Anal* **16**: 470–478.

Mauger AR, Jones AM, Williams CA. 2010. Influence of acetaminophen on performance during time trial cycling. *J Appl Physiol* **108**: 98–104.

Nahrstedt A, Schmidt M, Jaggi R, Metz J, Khayyal MT. 2007. Willow bark extract: the contribution of polyphenols to the overall effect. *Weiner Mediz Wochenschrift* **157**: 348–351.

Nieman DC, Shanely RA, Luo B, Dew D, Meaney MP, Sha W. 2013. A commercialized dietary supplement alleviates joint pain in community adults: a double-blind, placebo-controlled community trial. *Nutr J* **12**: 1–9. http://www.nutritionj.com/content/12/1/154.

Schmidt B, Ludke R, Selbmann HK, *et al.* 2001. Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: randomized placebo-controlled, double blind clinical trial. *Phytother Res* **15**: 344–350.

Shakibaei M, Allaway D, Nebrich S, Mobasheri A. 2012. Botanical extracts from rosehip (*Rosa canina*), willow bark (*Salix alba*), and nettle leaf (*Urtica dioica*) suppress IL-1β induced NF-κB activation in canine chondrocytes. *Evid Based Complement Altern Med*. DOI:10:1155/2012/509383.

Srivali N, Cheungpasitporn W, Chongnarungsin D, Edmonds LC. 2013. White willow bark induced acute respiratory distress syndrome. *N Am J Med Sci* **5**: 330–331.

Steinegger E, Hovel H. 1972. Analytical and biological studies on *Salicaceae* substances, especially salacin. II. Biological study. *Pharmaceut Acta Helv* **47**: 222–234.

Uehleke B, Muller J, Stange R, Kelber O, Melzer J. 2013. Willow bark extract STW 33–1 in the long-term treatment of outpatients with rheumatic pain mainly osteoarthritis or back pain. *Phytomed* **20**: 980–984.

Ulrich-Merzenich G, Kelber O, Koptina A, *et al.* 2012. Novel neurological and immunological targets for salicylate-based phytopharmaceurticals and for the anti-depressant imipramine. *Phytomed* **19**: 930–939.

Vlachojannis JE, Cameron M, Chrubasik S. 2009. A systematic review on the effectiveness of willow bark for musculoskeletal pain. *Phytother Res* **23**: 897–900.

Yuan M, Konstantopoulos N, Jongsoon L, *et al.* 2001. Reversal of obesity and diet induced insulin resistance with salicylates or targeted disruption of *Ikkβ*. *Science* **293**: 1673–1677.